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THE FIRST GEORGE FREDERIC STILL MEMORIAL LECTURE *

(DELIVERED TO THE BRITISH PAEDIATRIC ASSOCIATION, MAY, 1943)

SOME RECENT VIRUS WORK AND ITS PRACTICAL IMPORT

BY

S. P. BEDSON, M.D., D.Sc., F.R.S.

(Professor of Bacteriology in the University of London at the London Hospital)

May I say first of all how much I have appreciated being asked by your Association to give the George Frederic Still Memorial Lecture. I did not know Still but his record is, of course, familiar to me. To be chosen to inaugurate the lectureship instituted in Still's memory is an honour that I value very highly. And that your choice should have fallen on a laboratory worker gives me particular satisfaction since it carries with it the assurance that research of the kind that I have been doing, despite its academic flavour, is not without its appeal to those engaged in clinical medicine. It is perhaps not surprising that our knowledge of the viruses should have lagged behind that of the pathogenic bacteria or protozoa. The minute dimension of viruses, the difficulty with which they stain and the fact that they cannot be cultivated on lifeless media all contribute to making their study one of considerable difficulty. Despite the fact that the existence of such agents of disease was established in the nineties of last century by the work of Ivanowsky, Beijerink and Loeffler and Frosch, we have had to wait until recent times for any real advance in our knowledge of viruses. Prior to 1930 it was doubted whether even the largest viruses were visible with the microscope; those who held that this was possible were looked upon as somewhat misguided. And the same hesitation to accept what appeared most probable to some investigators was manifested by the majority in connexion with the immunological side of virus work. Whilst it was recognized that specific antibodies were elaborated in the course of virus infections, the rôle of these antibodies was relegated to one of very minor importance. It was held that, contrary to what had been found true of bacterial infections, immunity to a virus could only be established by infection; dead or inactive vaccines were useless for the purpose. Virus immunity was thought to be primarily a function of cellular change, a tissue immunity in which antibodies had little or no part and those in vitro serological reactions such as precipitation, agglutination and complement fixation, were considered inapplicable to virus study. There was, no doubt, a grain of truth in this, but in the main it was the outcome of misconceptions which the work of the last fifteen years has swept away. We now know that viruses can be seen or photographed; the larger ones are readily visible with an optical system similar to that in daily use in bacteriology. They can be cultivated in the laboratory, many of them with considerable ease. Even though they require living cells in which to multiply, the use of the developing hen's egg, a conception that we owe to the American pathologist Goodpasture, has provided a method of cultivation suitable to a large range of viruses which is within the reach of even the most modest laboratory. The serological reactions, and the complement fixation test in particular, are no longer considered inapplicable to viruses, in fact they are in daily use in the identification of viruses and the diagnosis of virus infections. Laboriously we have climbed to new vantage points. A new country lies before us which we have started to explore and it is my purpose in this lecture to tell you something of what we are finding. Obviously it would be impossible in the course of an hour adequately to survey all recent virus work; were I to attempt such a survey it would become little more than a catalogue. So I have decided to limit myself to a consideration of the recent work on three virus conditions: atypical pneumonia, herpetic infections and poliomyelitis. All this work is of considerable interest and of practical importance, furthermore, it exemplifies many of those advances to which I have already made general allusion.

Atypical Pneumonia

During the last three or four years the condition known as primary atypical pneumonia has been much in evidence here and elsewhere. In this country it has occurred in small epidemics both in the civilian population and in the services. The patient presents, with fever, headache, a non-productive cough and with little in the way of

* See p. 155.

physical signs in the chest. Skiagrams of the chest reveal a patchy pneumonia giving shadows of little density which may be lobar in extent. Bacteriological investigation of the sputum gives us information of negative value only, the total white count is normal or there may even be a leucopenia and since, in addition to these findings, the patient does not usually show any response to treatment with sulphapyridine, it has been assumed that the causal agent or agents belong to the group of viruses. Some workers have suggested that this is a new disease but it seems clear that the condition existed prior to the war though cases of it were then less numerous. The war conditions have favoured its spread; outbreaks have occurred in most parts of the country and our attention has been focussed on a condition to which in the past scant attention was paid since it was seen so infrequently. It is neither new nor is it due to a single cause, in fact the evidence available suggests that quite a number of different viruses are capable of producing this condition. Of these, the virus of psittacosis is the best known and most studied and although it appears to be responsible for only a relatively small proportion of cases of atypical pneumonia, I propose to speak of it first because of the many interesting facts which recent work on this virus has brought to light.

Psittacosis. In human cases of psittacosis, infection enters by the respiratory tract and in a considerable percentage of the clinically obvious infections, some degree of pneumonitis occurs. As in any infective process, the laboratory investigation of psittacosis should be directed primarily to the isolation of the causal agent and this can be achieved by the inoculation of mice with sputum. Not uncommonly, however, this investigation is not possible owing to an absence of sputum which is hardly ever profuse in this disease; or the investigation, though made, may give a negative result. In such cases one has to rely on the indirect evidence of infection given by serological tests with the patient's serum and of these tests the complement fixation reaction is the most satisfactory. Eight or nine years ago when at the London Hospital, we were beginning to use this test in the diagnosis of psittacosis (Bedson, 1935) the antigen employed was an unheated saline suspension of virulent mouse spleen; the virus was present in a fully active state. That antigen has now been replaced by one which is not only more reliable but also perfectly safe to use. It was found (Bedson, 1936) that this virus contained at least two important antigens, one heat labile, being destroyed by temperatures above 60° C., whilst the other could withstand boiling (table 1). As the result of infection antibodies to both the heat-labile and heat-stable antigens are produced, the latter in considerably greater quantity. And although we do not know what part, if any, these antibodies to the heat-stable antigen play in the immunity to psittacosis virus, they constitute a reliable index of infection. This work has a dual importance. It has supplied us with an antigen which keeps unchanged for months or years and one which can be employed without risk of infection. In addition it has shown that a virus, like a bacterium, can be antigenically complex. The virus of psittacosis is not unique in this respect, in fact it is now known that many of the larger viruses have this complexity of structure. Not only do they look like miniature bacteria, but they are bacteria-like in their construction. When the virus of psittacosis was first discovered it was believed that its natural hosts were birds of the parrot family. It was recognized that other species of birds such as the canary and various finches were susceptible and might even be responsible for human infection, but until recently psittacine birds were held to be the sole reservoir of infection and the embargo on the import of parrots and parrakeets, instituted in 1930 in an attempt to control the disease in this country, was based on this assumption. Subsequent work has shown this to be incorrect. In 1938 cases of atypical pneumonia which had been occurring for some years in the Faroe Islands, were shown to be due to a virus identical with or very similar to psittacosis, infection coming from fulmar petrels which the Faroe Islanders used as a source of food (Haagen and Mauer, 1939). A year or so later similar infections in Iceland were traced to the same source (Bedson, 1940). This demonstration that two such dissimilar species of bird as the fulmar and parrots suffered from naturally occurring infection with this virus suggested that, quite possibly, the disease was much more widespread in birds than had at one time been thought. And this has been found to be the case. Recent work has shown that the pigeon may carry the infection (Coles, 1940; Pinkerton and Swank, 1940) and be the cause of human cases (Meyer, Eddie and Yanamura, 1942). A survey of the pigeon stocks in America has shown this infection to be widespread (Meyer, Eddie and Yanamura, 1942) and since it appears that a similar state of affairs exists in this country (Andrewes and Mills, 1943) human infections contracted from pigeons can be expected to occur, in fact there is some evidence that they do. Meyer and Eddie (1942) have also described a case of psittacosis in the wife of a poultry farmer in New Jersey whose stock had been suffering from an unknown epidemic disease subsequently shown to be psittacosis. So there is ample evidence that a considerable number of bird species suffer from a natural infection with this virus so much so that Meyer has suggested that the name psittacosis is no longer applicable and should be changed to ornithosis. Since Baker (1942) has recently described an infectious pneumonia in cats and kittens in America due to a psittacosis-like virus, an infection, apparently, which can be transmitted to man, it looks as though even the term ornithosis might not be sufficiently all-embracing! Be this as it may the fact remains that the host range of psittacosis is very much more extensive than any one imagined ten years ago and the practical significance of this is that contact with birds of the

TABLE 1

ANTIGENIC COMPOSITION OF PSITTACOSIS VIRUS AS DETERMINED BY COMPLEMENT FIXATION

Serum *		Antigens				
		Psittacosis †		Normal mouse spleen		Saline
Treatment	Dilution	Unheated	Boiled	Unheated	Boiled	
Nil	1/16	++++ / ++++	++++ / ++++	− / −	− / −	− / −
	1/32	++++ / ++++	++++ / ++++			
	1/64	++++ / +++	++++ / +++			
	1/128	++ / +	++ / +			
	1/256	+ / −	+ / −			
Absorbed with unheated antigen	1/16	+ / −	+ / −	− / −	− / −	− / −
	1/32	− / −	− / −			
	1/64	− / −	− / −			
	1/128	− / −	− / −			
	1/256	− / −	− / −			
Absorbed with boiled antigen	1/16	++++ / ++++	++++ / +++	− / −	− / −	− / −
	1/32	++++ / ++++	+ / −			
	1/64	++++ / +++	− / −			
	1/128	++ / +	− / −			
	1/256	+ / −	− / −			
Saline		− / −	− / −	− / −	− / −	− / −

* Psittacosis antiserum prepared in the guinea pig. † Prepared from the spleens of infected mice.
Readings made after 30 minutes at 37° C. (upper) and again after standing overnight at room temperature (lower).
Degree of complement fixation indicated by + signs, ++++ representing complement fixation.

FIG. 1.—Imprint from spleen of mouse 48 hours after intra-peritoneal inoculation of a highly virulent mouse-passage strain of psittacosis virus. Shows numerous free virus particles which are all in the stage of elementary bodies.
Giemsa's stain. × 1800.

FIG. 2.—Imprint from spleen of mouse made at same stage of infection as in Fig. 1. Shows an intracellular cytoplasmic colony of psittacosis virus composed of elementary bodies.
Giemsa's stain. × 1800.

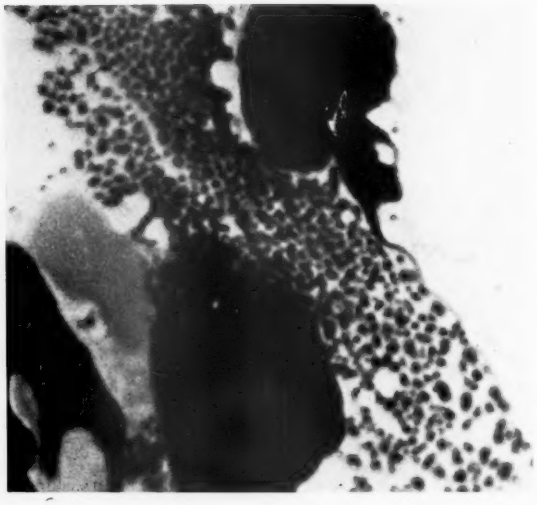

FIG. 3.—Imprint from spleen of mouse killed 24 hours after inoculation with the virulent passage strain of psittacosis virus. Only a portion of the virus is in the form of elementary bodies, larger forms are numerous and some of these appear to be dividing.
Giemsa's stain. × 1800.

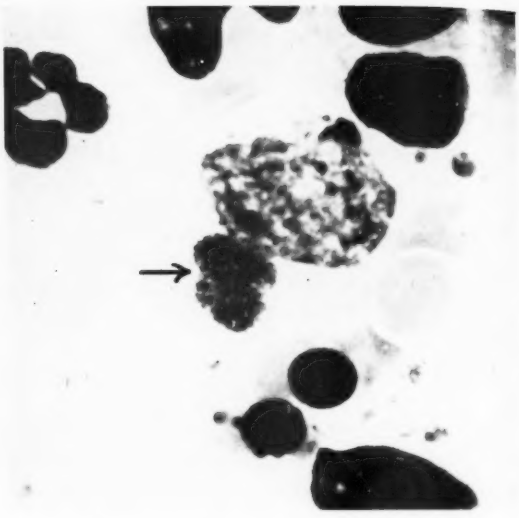

FIG. 4.—An intracellular colony of psittacosis virus in the spleen of a mouse killed 24 hours after inoculation.
Giemsa's stain. × 1800.

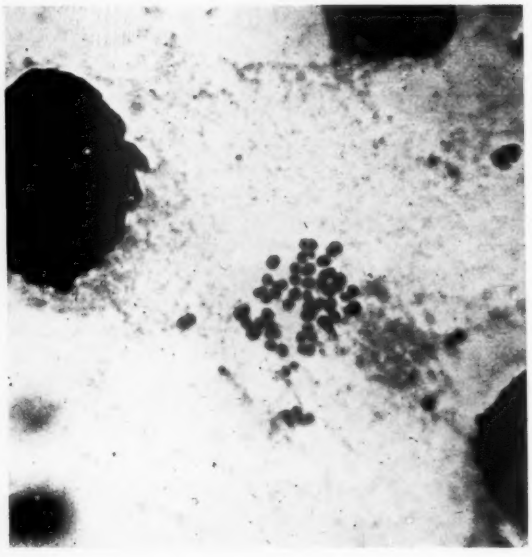

FIG. 5.—Imprint from spleen of mouse killed 16 hours after inoculation. No elementary bodies are found at this stage; the virus particles are all large. Shows a group of free large forms, one or two of which appear to be undergoing division.
Giemsa's stain. × 1800.

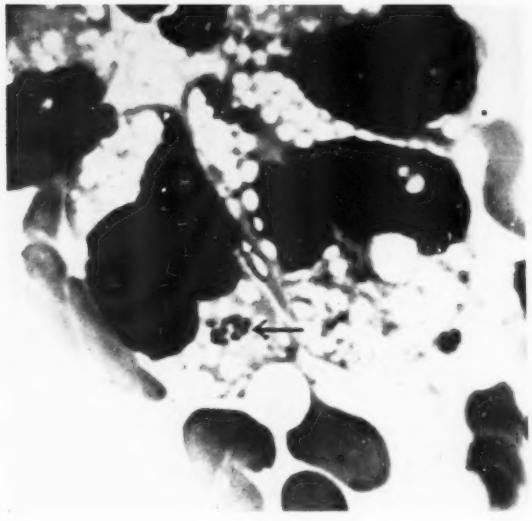

FIG. 6.—Imprint from spleen of mouse killed 16 hours after inoculation. Shows an intracellular colony of psittacosis virus composed of large forms.

parrot family is no longer an essential forerunner to the suspicion that a patient's illness is psittacosis. It should be pointed out that the strains of psittacosis virus isolated from these different sources, though showing some minor differences in their pathogenicity for experimental animals—the mouse and pigeon in particular—are morphologically and antigenically indistinguishable.

Relationship of psittacosis virus to other viruses with a similar morphology. Interesting though this work on the host range of psittacosis may be, the recent investigations on the relationship of this virus to other viruses of similar morphology are even more interesting and important. Psittacosis virus is one of the largest viruses, it stains readily with the method devised by Castañeda for the rickettsia and during multiplication undergoes a definite sequence of morphological change (fig. 1 to 6). Certain other viruses causing disease in man, the viruses of trachoma, of inclusion conjunctivitis

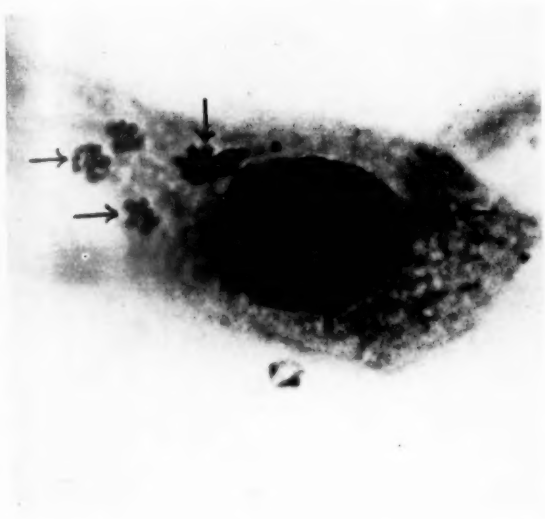

FIG. 7.—Conjunctival cell in smear from a case of inclusion blennorrhoea. The cell contains five virus colonies all composed of large forms.

Giemsa's stain. × 1800.

(Preparation by Dr. Phillips Thygeson, Iowa State University.)

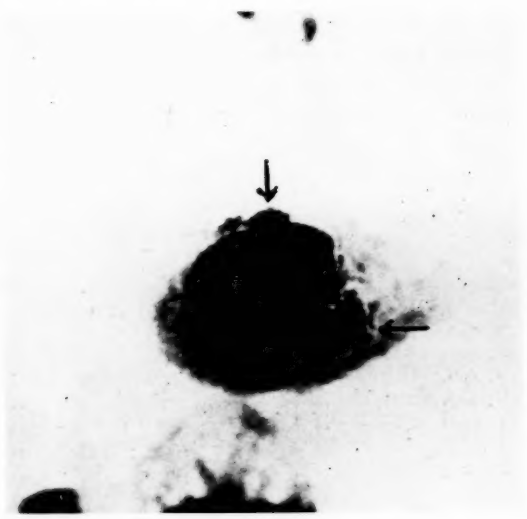

FIG. 8.—Conjunctival cell in smear from a case of inclusion blennorrhoea. The virus particles are of intermediate size.

Giemsa's stain. × 1800.

(Preparation by Dr. Phillips Thygeson, Iowa State University.)

FIG. 9.—Conjunctival cell in smear from case of inclusion blennorrhoea. The virus is in the form of elementary bodies and the cell, which is degenerate, is about to break down with the liberation of the virus particles.

Giemsa's stain. × 1800.

(Preparation by Dr. Phillips Thygeson, Iowa State University.)

(swimming-bath conjunctivitis) and of lymphogranuloma venereum have the same morphology and staining characters; they also show the same developmental forms as psittacosis (fig. 7 to 9). Since all these viruses stain by Castañeda's method, whereas other viruses do not, they might be termed the Castañeda-positive viruses; this staining method has a somewhat similar value to Gram's stain in bacteriology. In addition to the viruses I have mentioned the Castañeda-positive group includes two others recently isolated from man: the virus of meningo-pneumonitis of Francis and Magill (1938) and the virus isolated by Eaton, Beck and Pearson from cases of atypical pneumonia (1941). The former virus appeared in ferrets inoculated with the throat washings from a case of 'influenza,' its name is merely descriptive of the pathological changes to which it gives rise when injected into experimental animals by the appropriate routes. Eaton and his colleagues noted the similarity between their virus and the virus of meningo-pneumonitis; three of the six cases of atypical pneumonia studied by them gave a positive psittacosis complement fixation test and in two of them a rising titre was observed. In all probability the virus of meningo-pneumonitis and Eaton's atypical pneumonia virus are strains of psittacosis virus of pigeon origin. But the close resemblance shown by other members of the Castañeda-positive group to psittacosis virus has induced Rake and Eaton and their colleagues to see whether this resemblance was only superficial or whether it denoted any real relationship. It was found (Rake, Eaton and Shaffer, 1941; table 2) that the sera from human infections with the viruses of psittacosis, lymphogranuloma venereum and the virus isolated by Eaton et alia from atypical pneumonia all cross-reacted when examined by the complement fixation test with these three viruses. Furthermore they showed that five out of eight of the cases of atypical pneumonia under investigation gave a positive Frei test (see table 2). The close relationship thus revealed between these three viruses found further confirmation in cross-immunity experiments in animals (Eaton, Martin and Beck, 1942). This investigation, which included in addition to the above three viruses the virus of

TABLE 2

(From Rake, Eaton and Shaffer, 1941)

CROSS REACTION IN COMPLEMENT FIXATION TESTS WITH SERA AND ANTIGENS OF PSITTACOSIS, MENINGOPNEUMONITIS AND LYMPHOGRANULOMA VENEREUM

Serum	Case	Complement fixation titre with antigen from virus of		
		Psittacosis	Meningopneumonitis	Lymphogranuloma venereum
L.G.V. No. 9	Lymphogranuloma venereum		16	>240
L.G.V. No. 31	,, ,,		8	120
L.G.V. No. 45	,, ,,		4	>120
L.G.V. No. 51	,, ,,	32		>120
L.G.V. No. 60	,, ,,	256		>120
L.G.V. No. 66	,, ,,	128		120
Ps. 7	,, ,,	+		>240
Ps. 11	,, ,,	++		>240
Rs	,, ,,		8	16
Pu	,, ,,		32	32
A.R. 11	Psittacosis	++		480*
A.R. 13	,,	++		240*
A.R. 18	,,	++		120*
Ps. 1	,, (pigeon)	+		<15
2	,, ,,	++		480
3	,, ,,	+		120
4	,,	+		>240
5	,,	++		480
8	,,	++		>1920
9	,,	++		240
6	Pneumonitis	+		120
B †	,,	256	32	64
P †	,,	64	16	32*
Da	,,	32	8	30
Gu	,,		8	30
Rod.	,,	4	8	6
MG.	,,	256	16	32
LC.	,,		32	4
St ‡	,,		16	16
Mi	,,		64	32
Mey †	,,		8	32
Jo ‡	,,		64	16
Ma †	,,		8	8
Ra ‡	,,		16	32
Gr †	,,		8	8
W.P.M. †	Contact with pneumonitis		0	0
M.D.E. ‡	,, ,, ,,		0	0
O.B. †	,, ,, ,,		0	0

* Fixation also with soluble antigen of lymphogranuloma venereum. † Frei test positive.
‡ Frei test negative. + positive. ++ strongly positive.

meningo-pneumonitis, showed that whilst the immunity conferred by previous infection was greatest against the homologous virus, there was a considerable degree of immunity to reinfection with the heterologous viruses. But this is not all. Rake, Shaffer and Thygeson (1942) have found that this relationship extends even to the viruses of trachoma and inclusion conjunctivitis, for sera from cases of these diseases have fixed complement with a lymphogranuloma venereum antigen (table 3). Thus it appears that all the Castañeda-positive viruses are related. How close this relationship may prove to be we cannot say as yet, but it is sufficiently close to suggest that all these viruses have a common ancestry and that the specific differences which they possess have been acquired by prolonged residence in a particular animal species or a particular tissue, as in the case of the trachoma and inclusion conjunctivitis viruses. The implications of this work are of considerable importance. From the practical point of view it means that the serological reactions on which we have relied in the diagnosis of such conditions as psittacosis and lymphogranuloma venereum have lost their specificity; a positive and rising reaction merely entitles us to the conclusion that we are dealing with infection with one of a group of viruses and more than ever the laboratory findings will have to be interpreted in the light of the clinical and epidemiological findings. Similarly the Frei test loses much of its specificity. Viewed from the more academic angle the demonstration of the close relationship of the viruses of psittacosis and lymphogranuloma venereum, trachoma and inclusion conjunctivitis with the suggestion that they are derived from a common ancestor, is no less interesting. It

TABLE 3

(From Rake, Shaffer and Thygeson, 1942)

RESULTS OF COMPLEMENT FIXATION TESTS WITH LYMPHOGRANULOMA VENEREUM ANTIGENS AND SERA FROM CASES OF TRACHOMA OR INCLUSION CONJUNCTIVITIS

Patient	Institution	Eye infection		Serum titre in complement fixation tests † vs. Lg. V.		Frei test
		Stage ‡	Duration	Elementary bodies	Soluble antigen	
Ga	E.I.	III	> 10 years	6		
E.B.	,,	IIa	6 months ?	60	30	Negative
M.St.	,,	III	> 5 years	30	15	
L.Z.	,,	III	> 6 ,,	15	6	
R.R.	,,	III	> 5 ,,	< 6	15	
L.C.	,,	III	> 10 ,,	30	15	
D'A.	,,	III	> 15 ,,	15	30	
F.S.	,,	I		< 6	6	
Y.L.S.	,,	IV		6	—	Negative
S.U.	,,	IV		6	—	,,
M.T.	,,	IV		15	—	,,
We.	,,	IV		15	—	,,
V.B.	L *	I		6	6	,,
J.C.	,,	III		< 6	6	,,
N.G.	,,	IIa		< 6	< 6	,,
J.L.	,,	III		< 15	15	,,
C.M.	,,	III		< 6	< 6	,,
E.P.	,,	III		6	15	,,
S.S.	,,	III		15	6	,,
H.S.	,,	IIa		15	15	,,
St.V.	E.I.	Inclusion conjunct.	3 weeks	60	—	,,
G.D.	,,	,, ,,	2 ,,	6	6	

* The serum from 6 other feeble-minded trachomatous patients in the same cottage in institution 'L' were tested but were either anticomplementary or gave non-specific fixation with the antigen controls prepared from normal yolk-sac.

† Fixation 1½ hours at 37° C. + overnight at 2° C.

‡ MacCallan's classification: Stage I, incipient trachoma, stage II established trachoma, IIa follicular hypertrophy predominant, IIb papillary hypertrophy predominant, III cicatricial trachoma, IV arrested trachoma.

is true that such a thing is not unique in the virus world since the same appears to be the case with the pock viruses. None the less it serves to emphasize a state of affairs with which we are familiar in the bacteria and other micro-organisms and it is surely further evidence of the micro-organismal nature of viruses.

Response of viruses to sulphonamides. In this respect the behaviour of some of the Castañeda-positive viruses to sulphonamides is of interest. The available evidence goes to show that the action of these drugs on bacteria is indirect; they compete with a bacterial enzyme for an essential metabolite. The viruses of trachoma and lymphogranuloma venereum appear to be susceptible to sulphonamides and although it is stated (Meyer and Eddie, 1942) that infections with psittacosis virus do not respond to this form of chemotherapy, I have seen two cases treated with sulphapyridine and one with sulphadiazine in which a dramatic response was obtained. But even though the question of the susceptibility of psittacosis virus to sulphonamides is still in doubt, the fact that two viruses of this group do respond to these drugs is of considerable interest, for, unless the sulphonamides have some other mode of action, it means that viruses like those of trachoma and inclusion conjunctivitis have sufficient metabolic activity, independent of the cells which they infect, to render them open to attack by a sulphonamide. And this implies that they are micro-organismal in nature.

Other viruses causing atypical pneumonia. As I have already pointed out the psittacosis group of viruses probably plays only a minor part in the causation of atypical pneumonia. What proportion of cases occurring to-day are due to psittacosis it is difficult to say, but in a recent paper Smadel (1943) produces evidence that 10 of 45 cases of sporadic atypical pneumonia from eastern urban populations in the U.S.A. were psittacosis. In this country the incidence, as judged by my own observation, appears to be lower. What of the remainder? Have we any idea as to their etiology? It has been suggested that the virus of lymphocytic choriomeningitis might be responsible for some cases of atypical pneumonia. Smadel (1943) obtained no evidence of this, though my serological findings suggest that this virus, which is an important cause of aseptic meningitis in man, may occasionally give rise to atypical pneumonia. As to other claimants to

this rôle, we have the virus of Weir and Horsfall (1940) to which the mongoose alone of experimental animals appears susceptible and the virus which Eaton, Meiklejohn, Van Herrick and Talbot (1942) claim to have isolated from atypical pneumonia by inoculation of the cotton rat. Further work alone can decide what part these viruses are playing in the causation of this disease.

Herpes

You may be surprised that I should trouble to refer to a virus causing so trivial a condition as herpes. I do so because of the interesting new light which recent work has thrown on the natural history of this disease. The vesicular eruption of herpes occurs on the skin at muco-cutaneous junctions, the lips being the commonest site. The specific virus which causes it is of medium size and gives rise to typical nuclear inclusions in the cells which it infects similar to those produced by its near relatives, the virus of pseudo-rabies and B virus (fig. 10). A

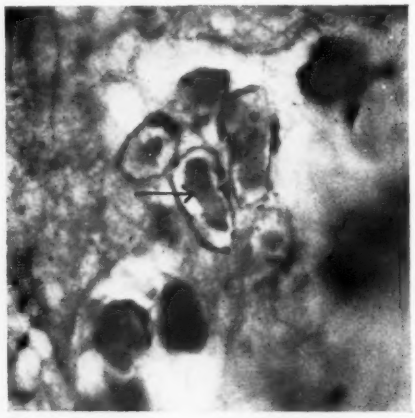

FIG. 10.—Section of herpetic lesion of guineapig's skin showing nuclear inclusions of Type A. × 1800.

peculiar feature of herpes is that it does not appear to be infectious. Herpetic eruptions are a symptom of a variety of conditions of which artificial fever, however induced, is the most herpetogenic. Some individuals are subject to herpes, others never get it; the source of the trouble seems to be intrinsic rather than extrinsic as in other infections. This apparent anomaly has led some investigators to postulate that herpes virus is generated spontaneously in the human tissues as the result of some derangement set up in the cells by those factors which precipitate an attack of herpes. Doerr, the Swiss virus expert, is the leading exponent of this view. The conception of spontaneous generation even of an agent so intangible as a virus has not met with ready acceptance by bacteriologists, and it has always seemed to me that a more rational explanation of the facts would be that certain individuals were asymptomatic carriers of herpes virus, and that when they were subject to one or other of the herpetogenic factors the balance between host and parasite was so upset as to allow the virus temporarily to gain the upper hand and for the infection to become apparent. Even some years ago there existed evidence in support of this view for Levaditi and his colleagues claimed to have demonstrated herpes virus in the saliva of herpetic subjects at a time when no labial eruption existed (Levaditi, 1926). More recently additional evidence in support of this hypothesis has come to hand. Andrewes and Carmichael (1930) and Brain (1932) have shown that a considerable percentage—up to 70 per cent.—of the hospital class of individuals possess herpetic antibody in their serum and, what is much more important, that there is a close correlation between possession of antibody and being subject to herpetic attacks (table 4). We have had to wait until quite

TABLE IV

HERPETIC ANTIBODY IN HUMAN SERA

Source of serum	Number	Complement fixation test with herpes serum	
		Positive	Negative
Individuals with herpetic lesions or reliable herpetic history ..	32	30	2
Individuals with a negative herpetic history ..	16	0	16
Individuals receiving protein shock therapy:—			
(*a*) developing herpes ..	4	3	1
(*b*) not developing herpes	6	0	6

(Compiled from figures given by Brain, 1932.)

recent times, however, for the final and convincing proof of this hypothesis and the overthrow of the conception of spontaneous generation as applied to herpes virus. In 1938, Dodd, Johnston and Buddingh published their observations on vesicular stomatitis in infants and young children. They demonstrated that this was an herpetic infection quite unlike anything one saw in older children and adults and they put forward the view that it represented a primary infection with herpes virus as the result of which a carrier state was set up. This carrier state, they postulated, continued throughout life, remaining entirely asymptomatic unless the individual was subjected to one of those factors which precipitate an attack of herpes when the virus gained the upper hand and gave rise to an herpetic eruption. They further postulated that after the age of two or three years, a physiological insusceptibility to infection with herpes virus developed so that if an individual had not been infected by that time he or she would be unlikely to contract the infection and so not become a herpes carrier and a herpetic subject. The researches of Burnet and

TABLE 5

(From Burnet and Williams, 1939)

PRIMARY HERPES INFECTIONS IN CHILDREN *

Patient	Age in years	Rabbit test: Keratitis †	Rabbit test: Antibody	First serum sample: antibody	Second serum sample: Days after collection of first specimen	Second serum sample: Antibody
de Y. ..	2	+++	0·007 per cent.	Nil (70 per cent.)	23	+ (2·1 per cent.)
Bag. ..	$1\frac{8}{12}$	+++	0·016 ,,	Trace (20 ,,)	34	+ (0·75 ,,)
Vin. ..	1	+++*, +++	0·05 ,,	Nil (100 ,,)	34	++ (0·035 ,,)
Gup. ..	$2\frac{1}{2}$	++	0·01 ,,	Nil (52 ,,)	20	+ (0·67 ,,)
McF. ..	3	+++	0·05 ,,	Nil (67 ,,)	—	++ (0·2 ,,)
O'T. ..	10	—		Nil (110 ,,)	20	+ (2·7 ,,)

* Herpes antibody is expressed as the percentage to which the activity of the virus is reduced by being mixed with undiluted serum under standard conditions; the smaller the value, the more potent is the serum.

† Under 'keratitis' the number of *plus* signs indicates the degree of purulent inflammation, * indicating death from specific encephalitis.

Williams (1939) in Australia have given complete confirmation of this work. They have found, just as Dodd and his colleagues did, that an herpetic stomatitis occurs in infants and young children and that this represents a primary herpetic infection since specific antibodies are absent in the early stages of the disease but develop with recovery (table 5). They have further shown that the percentage of adults with herpetic antibody in their serum varies in different social groups, being very much higher in the hospital class of individual than in those drawn from the higher social grades (table 6).

TABLE 6

(From Burnet and Williams, 1939)

PROPORTION OF 'POSITIVE' and 'NEGATIVE' TYPES OF SERUM IN DIFFERENT SOCIAL GROUPS

Group	'Positive'	'Negative'	Percentage 'Positive'
A. University graduates	10	17	37
B. Non-graduate laboratory workers ..	13	9	59
C. Hospital patients	51	4	93
D. Children and adolescents * ..	56	4	93

* In group *D* there were five specimens of serum giving intermediate values of 0·1 per cent. to 2·5 per cent. These are not included.

This is just what one would expect because it would be in those children reared under the poor conditions found in families with a low standard of living that the chance of a primary herpetic infection occurring in the early years of life would be the greatest. The only piece of evidence that is missing is the situation in which the herpes virus is carried; that awaits discovery. This work strikes me as extraordinarily interesting. It shows how in an animal a virus can enter into so well balanced a symbiosis with its host as to give little or no evidence of its presence unless that balance is upset in some way or another. Furthermore it renders unnecessary that unhappy suggestion that a virus can be generated spontaneously and gives further proof that viruses are most probably organized agents of a nature similar to other micro-organisms.

Poliomyelitis

Finally, I wish to say a word or two about poliomyelitis and in particular to draw your attention to some recent work which has revolutionized our ideas on the mode of spread of this disease. The virus of poliomyelitis is one of the smallest viruses and it is a confirmed neurotrope; nerve cells alone provide an environment suitable for its multiplication. Ten years ago one would have said with confidence that this disease was spread in the main by infective droplets and that the portal of entry of infection was the nasopharynx, the passage of virus from this situation to the central nervous system being via the olfactory hairs to the cells in the olfactory bulb and thence by axonal routes to the cord. This conception was based on certain well-established observations. In human cases of poliomyelitis the virus is to be found in the central nervous system and in the nasopharynx; it is never found either in the blood stream or in the cerebrospinal fluid. The monkey can be infected by applying the virus to the olfactory mucosa and in such experimental animals the olfactory bulb is the seat of histological change, showing that the virus has passed that way en route for the cord. What is more, if the connexions between the olfactory bulb and the olfactory mucosa are severed before one attempts to infect the monkey by the nasal route, infection does not take place; the pathway of the virus to the cord is severed. The same is true apparently if the monkey receives the virus intravenously, suggesting that, in the monkey at any rate, poliomyelitis virus passes from the blood stream to the central nervous system by the same route:

olfactory mucosa, olfactory hairs, olfactory bulb. Since there seemed little reason for doubting the accuracy of these observations it is not surprising that the conception of poliomyelitis as a disease spread by droplets should have received general acceptance. It is true that there were a few dissentient voices, Toomey in particular holding that the portal of entry of infection was the alimentary tract, but the majority saw no reason for rejecting the more orthodox view. There was just one discordant fact: the seasonal incidence of this disease. Poliomyelitis has its major incidence in the late summer and early autumn which is not what one would expect in a disease spread by infective droplets, but this was conveniently overlooked or discounted since it appeared to be at variance with all the other evidence. The last few years, however, have seen a radical change in our conception of the mode of spread of this disease. Firstly the olfactory bulbs from human cases, when they have been examined, have shown a surprising absence of any histological changes. It has been suggested that this might merely mean that in man the virus left less trace of its transit through these structures than in the monkey, but in the light of more recent work, demonstrating the presence of the virus in the stools of human cases and contacts, which will be referred to later, it acquires a greater significance. In the second place, recent field trials in N. America of the use of chemical sprays in the prophylaxis of poliomyelitis in man (Lennette, 1937) have given negative results. I should perhaps explain that experimental work in the monkey had shown that treatment of the olfactory mucosa with chemicals such as tannic acid, picric acid or zinc sulphate, protected the animal against infection with poliomyelitis virus when it was instilled into the nasopharynx. It was felt that the chemical spray offered great possibilities as a practical procedure in the control of poliomyelitis and the disappointing results obtained in field trials with this measure have only gone to strengthen the view that our conceptions as to the mode of spread of this disease were incorrect.

In the past, the occasional presence of the virus in the faeces of human cases of poliomyelitis has been reported. Kling, Wernstedt and Petterson (1911–12) claimed to have isolated poliomyelitis virus from such material with some regularity and Harmon and Levine (1936–7) obtained it from rectal washings in four cases. But the majority of workers obtained negative results and it was concluded that although the virus might be found in the stools, this was only an occasional happening and was not comparable with the regularity of its presence in the upper respiratory passages. But recent work has shown that this is not so. The studies of Paul and Trask and their colleagues have demonstrated that, given an adequate technique, the virus of poliomyelitis can be found in the stools of human cases with considerable regularity (Trask, Vignec and Paul, 1938; Trask, Paul and Vignec, 1940). What is more they have been able to show (Paul, Trask and Gard, 1940) that the sewage of urban communities in which poliomyelitis was

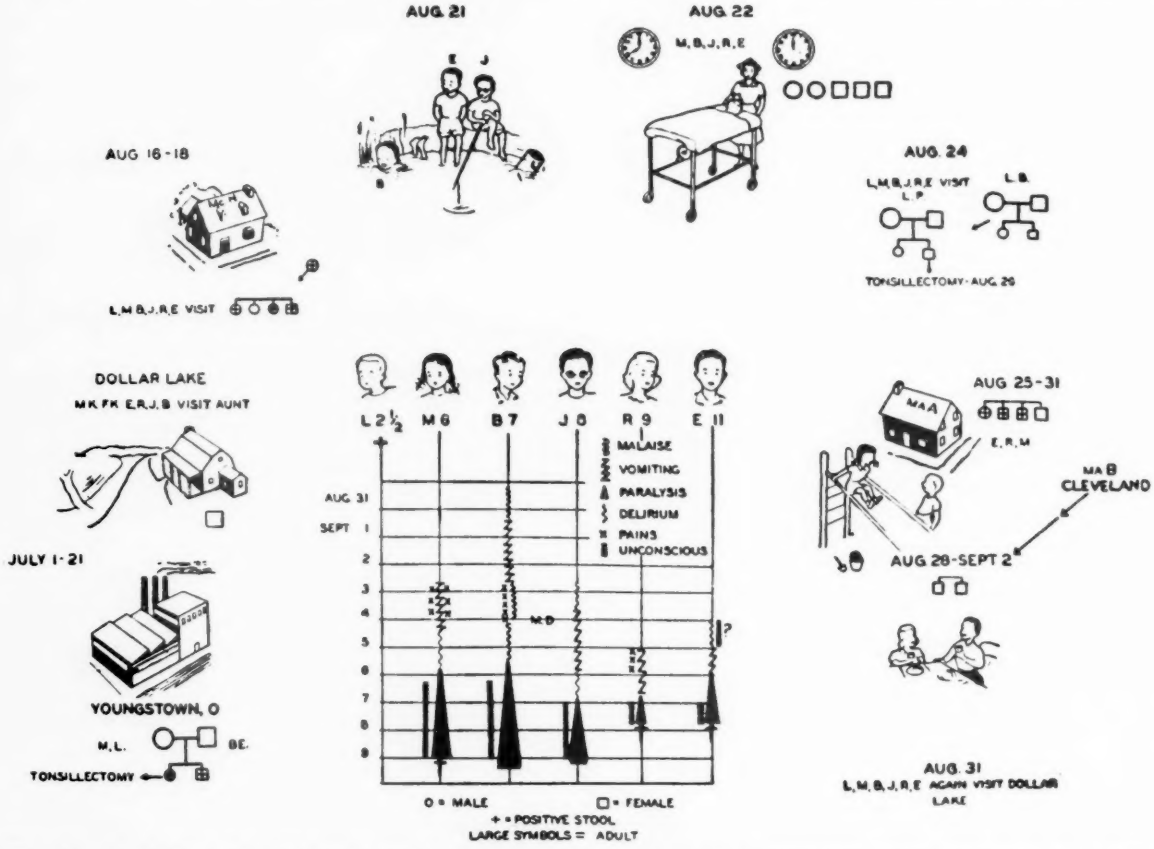

FIG. 11.—Activities of the K family and distribution of virus among their associates (from Francis et. al., 1942).

epidemic might contain the virus, whereas this was not so when poliomyelitis was not occurring. The importance of this mode of excretion of the virus has received ample confirmation from American work (Piszczek, Shaughnessy, Zichis and Levinson, 1941; Francis, Krill, Toomey and Mack, 1942). In the investigation of a small outbreak by Piszczek and his colleagues the virus was isolated from the stools in three out of four cases and from six out of thirty-four contacts, whereas the stools from fourteen non-contacts were negative. Francis and his co-workers (1942) report their findings in five cases of poliomyelitis of the bulbar type which developed in the children of one family all of which underwent tonsillectomy at the same time; three of them died (fig. 11). There were six children in the family; everyone had poliomyelitis virus in the stools. The stools of forty-three contacts of these six children were examined. Nine of these contacts were adults; none had positive stools. Of the child contacts, six were close contacts whilst in twenty-eight the contact had been less intimate. The six former children were all found to have virus in the faeces, but only four of the less intimate contacts provided positive results. There is thus an abundance of evidence of this mode of excretion of the virus in human poliomyelitis and this fact, together with the other evidence I have mentioned—the absence of histological changes in the olfactory bulbs and the failure of chemical sprays in prophylaxis—suggest most strongly that the usual route of infection is the alimentary and not the respiratory tract. This is not to say that the disease cannot be or never is spread by infective droplets, but only that if this mode of spread does occur, it does so uncommonly. Nor does the acceptance of the alimentary route of infection imply that invasion invariably takes place from the intestinal tract. In fact, Faber and Silverberg (1942) have described how one of their experimental monkeys which had received virus in fat-coated capsules, had its tongue gently swabbed with virus and had received a high enema of virus all without effect, finally developed poliomyelitis after having virus sprayed on to the throat, the olfactory mucosa having previously been blocked by spraying with zinc sulphate. The histological evidence showed that in this monkey the virus had reached the bulb by the intermediary of the IX and X nerves. So in all probability the virus entering by the alimentary route can pass to the central nervous system by a variety of routes at different levels; this would help to explain the distribution of the lesions in human cases. In any case the pathway to the brain or cord is via nerves—axonal—so that one would not expect the use of convalescent serum in the preparalytic stage of the disease, which surprisingly still has its advocates, to be effective; the virus would still be effectively protected against the action of antibodies.

The field of virus research is vast; what I have described to you this morning represents only a small corner of it. There are many equally important aspects of virus work that I might have chosen as the subject for this lecture. I hope, however, that what I have said has convinced you of the progress we are making, that we are gaining a better conception of the natural history of viruses and the diseases they produce and I hope also that it has not been without interest to you.

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STUDIES IN THE ANAEMIAS OF INFANCY AND EARLY CHILDHOOD

PART XIV.—THE FATE OF TRANSFUSED ERYTHROCYTES

BY

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The tendency of late years has been to consider the results obtained by transfusion of blood as giving the most reliable indication of the life of red cells and to disregard such results as have been obtained by other methods if found inconsistent with these.

The first transfusion experiments made with this object were carried out almost a century ago by Marfels and Moleschott and by Brown-Séquard (Hunter, 1884–6). In these experiments donor and recipient were taken from different species so that their red cells might easily be distinguished by their shape or possession of a nucleus. In the first experiments in which blood from the same species was used the fall in the red cell count was the only criterion, certainly an unreliable one, of the disappearance of transfused cells (Worm-Müller, see Hunter, 1884–6). Todd and White (1912) were the first to introduce a method for the differentiation of the donor's cells in the circulation of a recipient of the same species. Isohaemolytic serum placed in contact with R.B.C. of the individual for which it has been made is a specific reagent for these corpuscles and by making use of this fact these authors were able to follow the fate of red cells transfused from one bull to another. The transfusion, however, was followed by the development of haemolysins for the donor's cells in the serum of the recipient, a fact which invalidates the result.

Credit for the introduction of a method by which the cells of donor and recipient can be differentiated in human beings belongs to Ashby (1919, 1921) who transfused group O blood into group A recipients and counted those red cells which were not agglutinated by α-agglutinin serum before and at intervals after transfusion. These were the first of a number of similar experiments which, though they have been adversely criticized, are still regarded by many authorities as being the most convincing contribution to the solution of the problem. It must be emphasized, however, that later authors have drawn conclusions from Ashby's results which are quite different from those drawn by the author herself. Ashby stressed the wide variation, from 30 to more than 100 days, in the time for which the transfused cells persisted in the recipient's circulation. She did not believe that the red cell died because of its age, but assumed a process of active destruction by the organism leading to a cyclic elimination of the donor's cells. In quoting her work, however, many authors have accepted the longest time for which transfused cells were found to persist as the normal life span of erythrocytes, regarding it as unlikely that red cells transfused into another organism should thereby have their life prolonged. In this connexion it is worth mentioning that the same consideration induced Görl (1926) to contest the reliability of Ashby's method, the life span of R.B.C. deduced from these experiments being so much longer than that obtained by other methods, e.g. bile pigment excretions. Some of Görl's criticisms, which are supported by observations of Wildegans (1926), are certainly not without foundation. The fact that the number of unagglutinated cells in a single blood sample may vary between 25,800 and 368,000 per c.mm. according to the length of time and vigour with which the pipette is shaken does not encourage confidence in the method. It seems, however, that in the hands of a single investigator comparable results may be obtained. The most convincing proof that the unagglutinable cells after transfusion of group O blood to an A recipient are transfused cells in fact is given by the observation of Maizels and Paterson (1940) that the unagglutinated cells, filtered off after preliminary agglutination with α-serum, corresponded in their reactions to anti-M and anti-N serum with the donor's corpuscles.

Results similar to those of Ashby have been obtained by Wearn, Warren and Ames (1922), Krjukof and Krilova (1935) and by Maizels and Paterson (1940); others, however, were able to trace the transfused cells for only a comparatively short time (Jerwell, 1924; Hotz, 1921; Kramarenko, 1928). A method which seems to be superior to Ashby's test has been introduced by Woronow (1936). By repeated small intravenous injections of group A or B blood into group O individuals a specific anti-A or anti-B haemolytic serum was obtained. This serum with added complement was used as a counting fluid after blood transfusions

from universal donors into A or B recipients. The serum haemolyzed the recipient's cells leaving only those of the donor. Unfortunately only two cases were reported. The survival of transfused cells was 19 and 35 days respectively. It is certain that the 'indirect differential agglutination test' of Ashby gives less reliable results than a 'direct differential agglutination test,' a method in which the transfused cells are detected by a serum which agglutinates these and leaves the recipient's cells unaffected. Using the four groups of human blood this test is only occasionally applicable in newborns in whom sometimes the serum does not contain agglutinins and blood of group A or B can therefore be used for a recipient of group O. Jerwell (1924) used this method in one case and followed the transfused cells for about six weeks. A wider field of application became available as the result of Landsteiner's discovery of M and N factors. With anti-M and anti-N serum Landsteiner, Levine and Janes (1928) followed the transfused cells for seven weeks. More extensive investigations with this method have been made by Martinet (1938), Dekkers (1939) and recently by Mollison and Young (1940). Dekkers was able to demonstrate the persistence of the donor's cells in the recipient's circulation by a macroscopic test for an average of 54½ days and by a microscopic test for 75½ days. Martinet considers that the macroscopic test only is reliable. The direct differential agglutination test allows the detection of very small amounts of transfused blood but it is possible only roughly to follow quantitatively the disappearance of transfused cells with this method. If, on the other hand, the indirect differential agglutination test is applied to the factors M and N the test for technical reasons becomes liable to the same objections as the original method of Ashby. Dekkers' figures indicate the time at which approximately all transfused cells had disappeared. It is probable, however, that the red cells produced on any day vary to some extent in quality and may be expected to survive for varying periods; observations supporting this view will be given later. If the standard deviation of the red cell population from this point of view be high, the time taken for the disappearance of all transfused cells may well be considerably longer than the average cell's life span. Apart from the intrinsic variations in the quality of R.B.C. the influence of environmental factors must be born in mind. The erythrocyte population may be compared with a human population in which a high percentage of the mortality is due to old age, yet 'if we were to view "natural death" as the termination of existence due to the uniform senescent atrophy of all the structures of the organism, leading to a uniform depression and ultimately simultaneous extinction of all its functions, then "natural death" in all probability never occurs' (Robertson). For the R.B.C. variations in the number of cells in the circulation on one and in the reservoirs on the other hand, variations in the oxygen consumption by the tissue (e.g. exercise) and formation of CO_2 leading to transient changes in pH are factors of which it can rightly be assumed that they exert a considerable influence on the life span of R.B.C. In experiments described in the previous paper (part XIII) it has been shown that the majority of R.B.C. formed at one time die at approximately the same time; old age is therefore the main cause of the erythrocyte's death. But if it were the only cause a linear disappearance of transfused cells would always be found. This was not so in most of Ashby's experiments. In experiments described below, a linear disappearance was observed only for a certain length of time.

Although for these and other reasons, which will be discussed below, transfusion experiments can only demonstrate the fate of transfused cells in various conditions, not the life span of normal cells, they afford a useful way of investigating many questions connected with the production and destruction of R.B.C. It was thought desirable therefore to follow the fate of transfused cells with other methods than the differential agglutination.

Two methods have been used in the course of these investigations: (1) the analysis and decomposition of Price Jones' curves in cases where the donor's and recipient's red cells formed distinguishable groups; (2) quantitative determinations of alkali-resistant and alkali labile haemoglobin after blood transfusions in newborns. It is obvious that each method has only a restricted field of application.

The simplest way to follow the fate of transfused cells is encountered in the case in which the recipient's R.B.C. population is completely replaced by the donor's cells. One such case has been observed: a baby with erythronoclastic anaemia of the newborn (already mentioned in part XIII). In chart I the solid curve represents the baby's red cell population before transfusions, the dotted curve the donor's R.B.C. population. After three transfusions the baby's Price Jones' curve (dashed curve) was found to be identical with that of the donor and at the same time reticulocytes practically disappeared from the peripheral circulation. In this aregenerative period there was a steady fall in the red cell count for six days at which time a fresh reticulocytosis occurred. Two days later the Price Jones' curve, which had remained unchanged up to the time of reticulocytosis, showed distinct signs of heterogeneity (chart II, dotted curve). The drop in the six days was from 3,520,000 to 2,300,000 or 34·7 per cent. (the figures for four counts in this period fell on a straight line), from which an average persistence of the transfused R.B.C. in the recipient's circulation of 17·3 days may be deduced. This conclusion is quite consistent with the appearance of the Price Jones' curve 15 days after transfusion for this fairly closely resembles the patient's original curve (dashed curve).

In order to compare the length of life of the transfused cells with that of the recipients's cells it is necessary only to estimate the time taken for the complete replacement of the recipient's cells by those of the donor. Unfortunately the second Price Jones film was taken six days after transfusions had been started. As this curve already corresponds to that of the donor's R.B.C. population it may be concluded that the baby's cells had a life span of

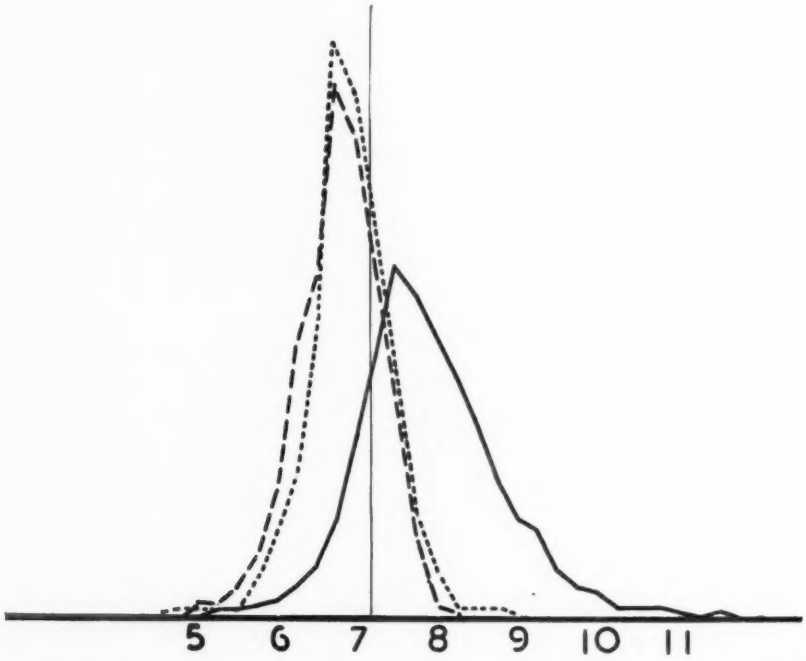

CHART I.—R.B.C. population of a case of erythronoclastic anaemia before transfusion (solid curve), after three blood transfusions (dashed curve) and this of the donor (dotted curve).

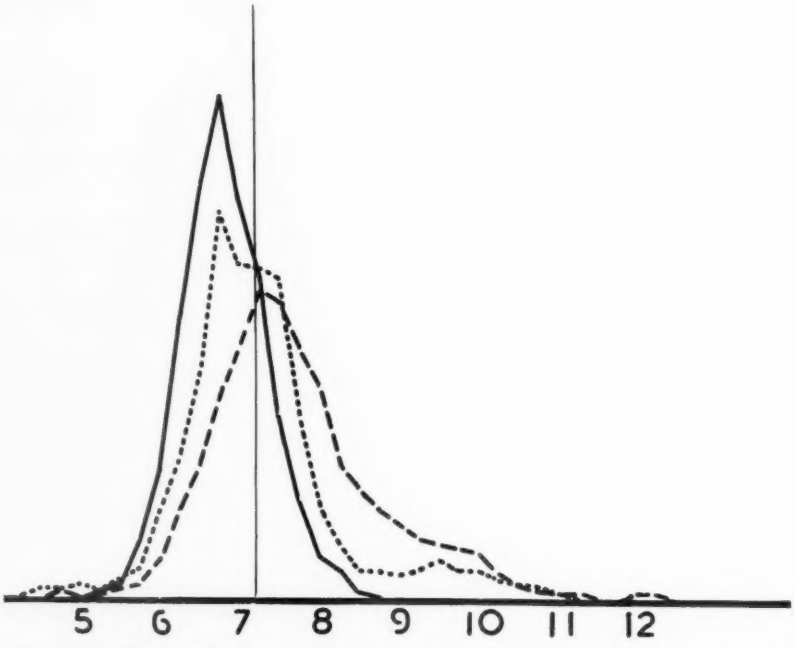

CHART II.—R.B.C. population of a case of erythronoclastic anaemia of the newborn during an aregenerative phase following 3 blood transfusions (solid curve), two days (dotted curve) and six days (dashed curve) after the start of reticulocytosis.

at the most six days. A further limitation of this time is possible if the figures for mean corpuscular volume are taken in account. The mean corpuscular volume decreased from $92\mu^3$ to $69{\cdot}5\mu^3$ within three days, that of the donor's cells being $68{\cdot}1\mu^3$ (two determinations: 68·0 and $68{\cdot}2\mu^3$ respectively). A life span of about three days for the baby's R.B.C. can therefore be assumed. No estimate of the reticulocyte maturation time having been made before transfusion it was not possible to form an estimate by this means until a fortnight after the last transfusion when red cell and reticulocyte counts were fairly constant for four days. The average reticulocyte count at this time was 13 per cent. and the maturation time eleven hours. The daily regeneration rate therefore was 28·4 per cent. and the life span 3·55 days. In this case, therefore, the transfused cells survived some five times longer than the recipient's cells yet their life was considerably shorter than that of normal cells in normal circumstances.* A similar selective

* The donor was the Rh–negative mother.

destruction affecting the recipient's cells to a higher degree than those of the donor was observed in a case of acholuric jaundice, mentioned in part XII, when two blood transfusions were followed by an aregenerative phase of six days. The replacement of the recipient's R.B.C. population by that of the donor was, however, in this case not complete.

Except in cases with complete replacement of recipient's cells by those of the donor such a simple analysis of Price Jones' curves is not a feasible way to follow the fate of transfused R.B.C. If the donors and recipient's cells differ considerably in mean diameter, however, a transfusion results in a heterogeneous distribution curve and for quantitative determination of the components representing the cells of donor and recipient in such cases a somewhat laborious decomposition is necessary. The mathematical foundation for decomposition of distribution curves has been laid by Pearson but a satisfactory and fairly simple way for a graphic decomposition has only recently been elaborated by Mogensen (1938). As some observations concerning the application of Mogensen's method for the decomposition of Price Jones' curves after blood transfusions can be only understood with the knowledge of the procedure, this method will now be briefly described.

A preliminary adjustment precedes the decomposition. For this purpose the sum of the numbers of cells present in two neighbouring classes of the original Price Jones' curve is taken as the number of cells belonging to one class, the diameter of which is the midpoint between the two classes. The result is a new distribution curve with 1000 cells instead of the original 500. The reason for making such an adjustment has been given by Pohle (1927): the width of the classes in a Price Jones' curve is $0{\cdot}25\mu$ but the measurements are made to the nearest of $0{\cdot}5\mu$. If all R.B.C. were perfectly circular the resulting distribution curve would represent a series of peaks separated by classes without any cells.

The adjusted curve is copied on tracing paper, the copy inverted and moved to and fro over the original till one covers the other as completely as possible, especially in the region of the peak. The midpoint of that part of the abscissa common to both curves represents the mean diameter of the main component. As the figures on the abscissa for the non-inverted curve run from left to right and for the inverted one from right to left the figure for this midpoint is not always identical for both abscissae and the arithmetic mean of the two figures must be taken in such a case. A graph is now constructed by plotting the squared differences between the mean diameter of the main component and the diameter of each class $(x_1 - M_0)^2$ against the logarithm of the number of cells found in the corresponding class (log n′) (chart VI). A series of points is obtained in this way and that line is drawn which touches most of the points in the lower right hand part of the chart, i.e. the points corresponding to the classes with the greatest numbers of cells. The standard deviation of the main component is proportional to the slope of this line. If, as in Mogensen's charts and in chart VII, the scale on the x-axis is twice the scale on the y-axis (0·5 abscissa = 1·0 ordinate) the slope of the line is 2 tan α. If the slope is b, the squared standard deviation $s^2 = 0{\cdot}217 \times b$. If a is the antilogarithm of the piece cut off the abscissa the number of cells belonging to the main component is calculated from the formula: $N = 5{\cdot}013 \times a \times s$ or $5{\cdot}013 \times \sqrt{0{\cdot}217b} \times a$. Having now obtained the main characteristics of the main component the number of cells expected in each class of an ideal distribution curve having the mean diameter and the standard deviation of the main component can be calculated with the aid of a table of areas of the normal distribution curve: $Q(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} dx\, e^{-\frac{x^2}{2}}$. In Charlier's book this table is found on p. 121. The procedure is best explained by an example given by Mogensen. The number of cells expected in the class interval with the midpoint 8·50 is to be calculated for a population with a mean diameter of 8·850 and a standard deviation of 0·737. The limits of this class are 8·375 and 8·625. The deviation of these points from the mean diameter (M_0) are $-0{\cdot}475$ and $-0{\cdot}225$ respectively. These deviations are expressed as multiples of the standard deviation $\left(\frac{x_1 - M_0}{S_0}\right)$ which in this case gives $\frac{8{\cdot}375-8{\cdot}850}{0{\cdot}737}$ and $\frac{8{\cdot}625-8{\cdot}850}{0{\cdot}737}$ or $-0{\cdot}644$ and $-0{\cdot}305$. Two figures are now looked up in the table of areas: the area of the distribution curve to the left of $-0{\cdot}644 = 0{\cdot}2597$ and the area to the left of $-0{\cdot}305 = 0{\cdot}3801$. The difference between these two figures (0·1204) is the area between the two limits, and this when multiplied by the number of cells belonging to the main component (N_0) gives the number of cells which out of the total number (N_0) on average are placed in the class with the diameter 8·5. In normal homogeneous curves the agreement between the expected number and that found by actual cell measurement is very close, whilst in cases with two components, e.g. a minor component with a mean diameter smaller than that of the main component agreement is only found near to the mean diameter of the main component and to the right of this. In the classes with smaller diameters the original Price Jones curve shows more than the expected number of cells; by subtraction an approximate distribution curve of the minor component can be constructed.

Applying this method to the decomposition of bi-apical Price Jones' curve, such as may occasionally be encountered after transfusion, only the higher peak, usually corresponding to the recipient's curve, should be taken into account in covering the original adjusted curve with the inverted one.

Occasionally the application of Mogensen's original method is impossible. Charts III and IV show two plateau-type curves, both cases of acholuric jaundice, that in chart III after a haemolytic crisis, that in chart IV after blood transfusion. In chart III there is a definite peak corresponding to the 'normal' microcytic component, whereas in chart IV (solid curve) there is no definite peak.

If in the first case $(x_1 - m_0)^2$ is plotted against log n, a line can be drawn, the slope of which is proportional to the standard deviation of the main component, as seen in chart VI. In the second case, however, a series of points is obtained on the right side of the chart lying on a line which forms an angle of 90° with the x-axis and would correspond to an indefinitely great standard deviation (chart VII).

This difficulty has been overcome in the following way: It was assumed that the main component

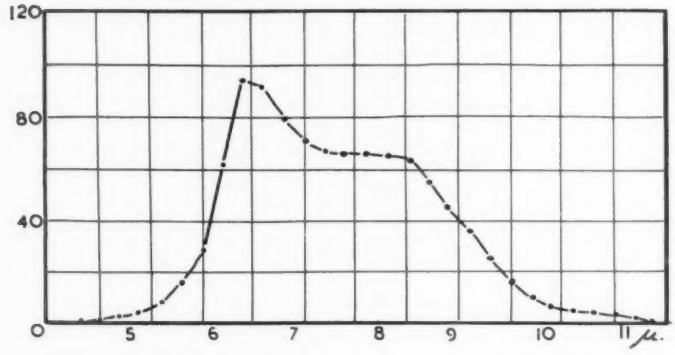

CHART III.—Adjusted distribution curve of R.B.C. in a case of acholuric jaundice (R.D.) after a haemolytic crisis.

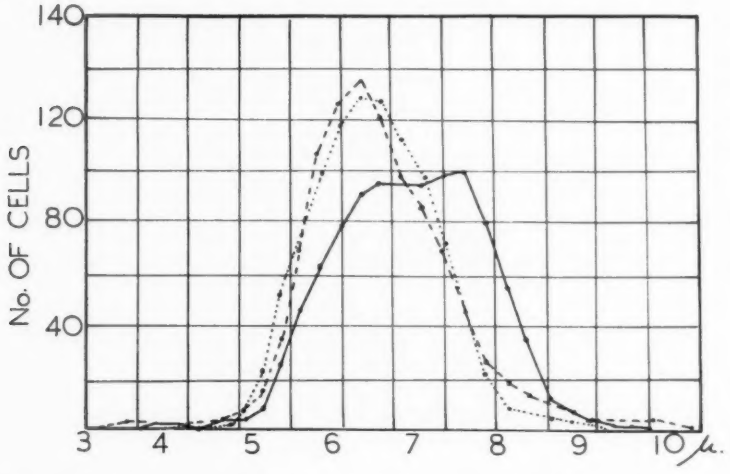

CHART IV.—Adjusted Price Jones' curves of a case of acholuric jaundice before transfusion (- - - -) . . . few hours after transfusion (————) and 17 days after transfusion (. . . . .).

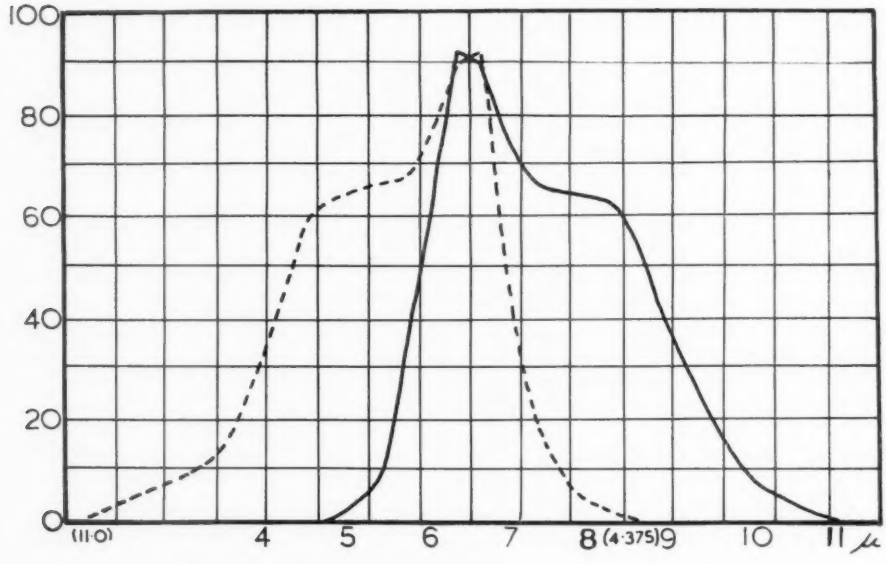

CHART V.—Adjusted Price Jones' curve of a case of acholuric jaundice after blood transfusion. ————Non-inverted, - - - inverted curve.

immediately after transfusion was identical with that of the recipient's R.B.C. population before transfusion. The mean diameter and standard deviaton of the main component can therefore be taken from the Price Jones' curve (or its main component) before

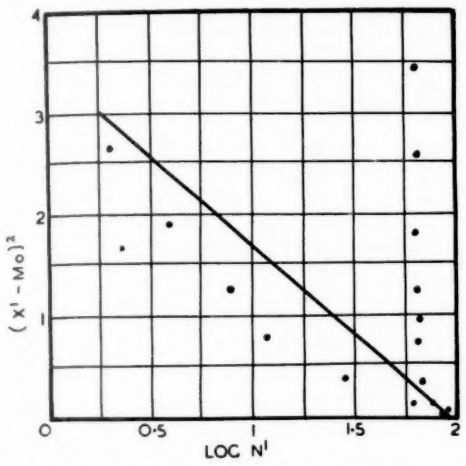

CHART VI.—R. D. Acholuric jaundice after transfusion. Mo = mean diameter of the main component = 6·50, x' = diameter of any class interval in the adjusted distribution curve, N' = the corresponding number of cells.

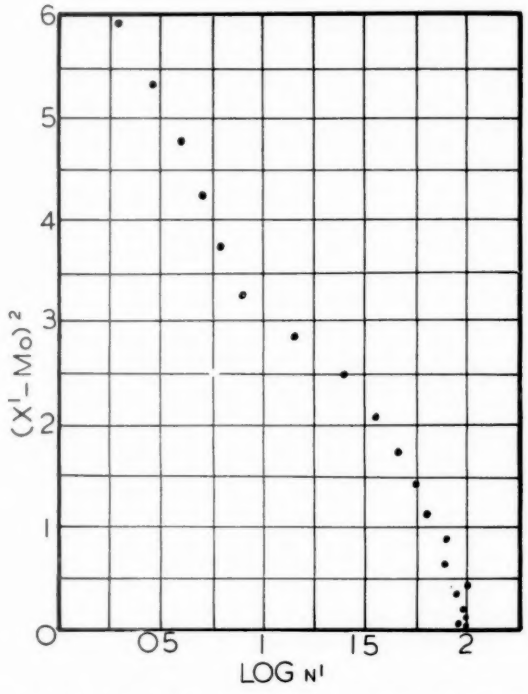

CHART VII.—V. M. Acholuric jaundice after blood transfusion. Decomposition of the erythrocyte distribution curve.

transfusion. The figure *a* is usually so close to the actual number of cells at the peak of the adjusted Price Jones' curve that the highest number of cells met in any of the classes after transfusion can be taken with but little error as being identical with *a*. Having thus the figures for s and *a* the number of cells in the main component can be calculated using the same constants as those given by Mogensen. In the case represented in chart IV the accuracy of this procedure has been checked, the number of cells in the main component (N_0) being almost identical with that expected from the amount of transfused blood and the child's blood-volume. Approximately one-third of the patient's red cells after transfusion have been those added by transfusion which would correspond to 167 cells out of 500. The decomposition gave 175 cells in the minor component.

The method of following the fate of transfused cells by changes in the Price Jones' curve is subject to more limitations than that of the necessary difference in the size between the cells of the donor and recipient. Except in the ideal case when regeneration is such that an exactly constant level of red cells is maintained throughout the experiment a correction must be applied for any changes in red cell level, for the minor component is expressed as the number of cells per five hundred of the whole; moreover any significant change in the distribution curve (mean diameter and standard deviation) of the recipient's cells make any conclusions on the disappearance of the minor component unreliable. Normally, apart from some degree of diurnal variation, the distribution curve shows a most striking constancy. This is probably true also in acholuric jaundice in periods of equilibrium between blood formation and destruction. Even in normal babies in the neonatal period on the other hand a change in the distribution curve takes place (van Creveld, 1932) which may be more marked in cases of macrocytic erythronoclastic anaemia (Hawksley and Lightwood, 1934). Exact matching of the mean diameter of major and minor components with those of the recipient's and donor's cells is not absolutely necessary. It can be assumed that changes in the numerical values of major and minor components run parallel to the disappearance of transfused cells as long as the main characteristics of the major component do not change during the period of observation.

TABLE I

NUMBER OF CELLS IN THE MAJOR AND MINOR COMPONENT OF THE RED CELL DISTRIBUTION CURVE AT VARIOUS DAYS AFTER TRANSFUSION OF NORMOCYTIC BLOOD IN TWO CASES OF ACHOLURIC FAMILY JAUNDICE

Case	Days after transfusion	Number of cells	
		Major component	Minor component
M.M.	0	324	176
	11	452	48
	29	494	6
V.M.	0	325	175
	7	395	105
	11	448	52
	17	492	8

Table 1 shows the figures for major and minor components in two cases of acholuric jaundice after transfusion with normocytic blood. The figures suggest that the transfused cells disappear within

three weeks. The life span of the cells of the recipient calculated from the reticulocyte count and maturation time was five and four days respectively. As in the case of erythronoclastic anaemia of the newborn described above, the red cell destruction was selective and the transfused cells evidently survived much longer than those of the recipient, though apparently not so long as the average normal cell. In a third case of acholuric family jaundice recently under observation, when two large transfusions were given in a haemolytic crisis and Price Jones' curves made daily for ten days and every second day for another three weeks, the transfused cells survived in the recipient's circulation just for three weeks. The finding of a short survival of transfused R.B.C. in acholuric jaundice suggests an abnormal activity of the blood destroying mechanism and is in agreement with the observations of Dekkers (1939), Placeo (1928) and Dedichen (1932), who by means of both Ashby's method and the differential agglutination test with anti-M and anti-N serum observed the disappearance of transfused cells from the blood of acholuric family jaundice in periods varying from a few to twenty-three days.

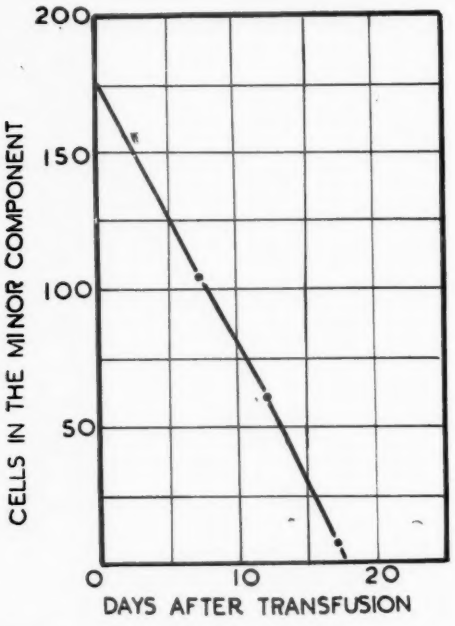

CHART VIII.—Elimination of transfused R.B.C. in a case of acholuric jaundice (V.M.)

Chart VIII indicates the rate of disappearance of transfused normal erythrocytes in one case of acholuric jaundice. The observed points follow a straight line, thus indicating that in spite of an increased activity of the destructive mechanism the cells are neither destroyed indiscriminately nor in proportion to their concentration. The most plausible explanation of this straight line is that while the duration of life of normal cells transfused to a case of acholuric jaundice is shortened, nevertheless, the cells die in relation to their age.

One of us (T.W.L.) has described elsewhere (1941) in detail a series of experiments in which blood from both an active and from cured cases of acholuric jaundice was transfused into normal persons. The results of the decomposition of the Price Jones' curves in one of these experiments are given in charts IX and X in which the major and minor components of a curve constructed shortly after transfusion are compared with the original curves of recipient and donor (chart IX) and the gradual disappearance of the minor component is shown (chart X).

The bulk of the transfused cells disappeared in about seven days when the donor was an active case and in some ten days when the donor had been completely relieved of symptoms by splenectomy some years before. It was observed that in the latter case the transfused cells became more spheroidal a few days after transfusion. It is apparent from these results that the red cell of active

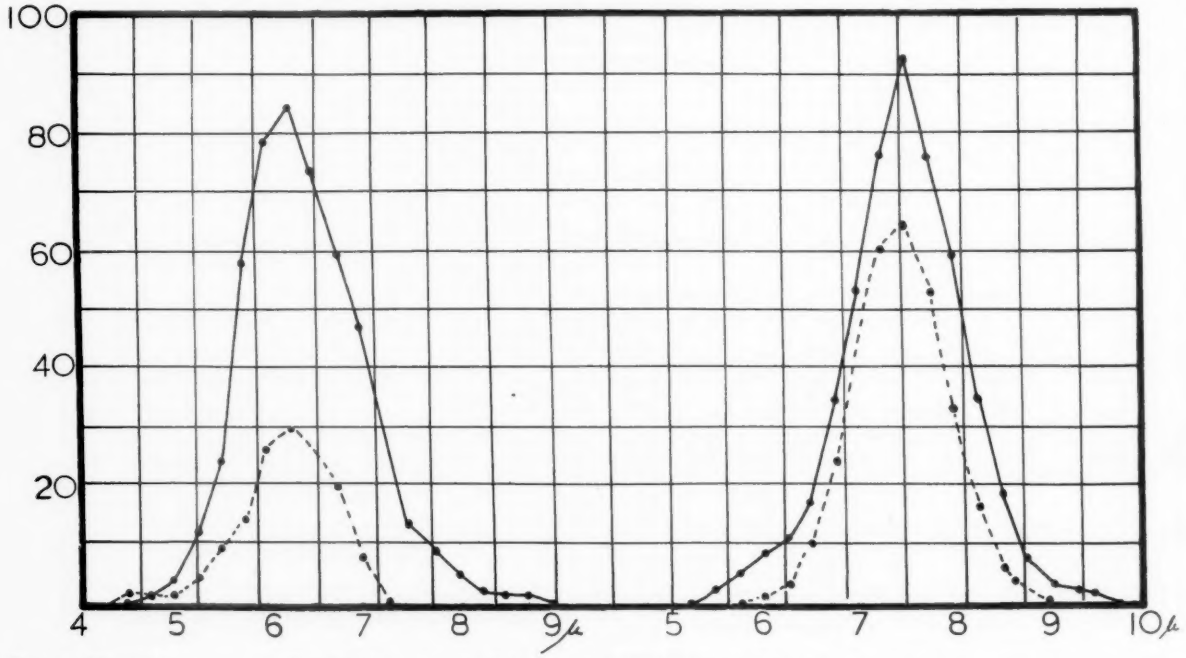

CHART IX.—(a) ——— distribution curve of the donor's (acholuric jaundice) red cell population, - - - - minor component of the recipient's red cell population after transfusion. (b) ——— recipient's red cell population, - - - - major component of the recipient's red cell population after blood transfusion.

acholuric jaundice has but a brief span of life whether in the patient's body or after transfusion into normal persons. Moreover, though after splenectomy abnormally rapid destruction ceases in this condition, the cells are still readily susceptible of destruction when transfused into a normal person.

The donor, who had active acholuric jaundice, had 14 per cent. reticulocytes with a maturation time of six to eight hours. The life span of his cells was therefore two to three days. It would seem that these cells were less readily destroyed by the normal individual than by the patient.

In these experiments the bulk of the transfused red cells disappeared rapidly and, in two cases, the figures for the minor component fell upon a straight line; in all, however, there remained a small microcytic minor component which persisted without change for some days. It seemed probable that a few of the transfused cells were considerably more resistant than the average, or for some other reason had persisted longer in the recipient's circulation than might be expected if the life span of all cells were identical. Similar observations are reported by Ashby (1919, 1921) and Jerwell (1924). They afford a firm basis for argument against the general assumption that the last of the donor's cells to disappear are always the youngest and that the time of their disappearance is equivalent to the average life of the red cell.

macrocytic population in icterus gravis and the donor's normocytic population is often not great enough to make the heterogeneity of the resulting distribution curve obvious. It must be realized that a distribution curve which appears homogeneous by Mogensen's analysis may yet be heterogeneous in fact. We have constructed from a series of distribution curves with different mean diameters summation curves which appeared to be homogeneous by Mogensen's decomposition. Even a curve practically identical with a Gauss-curve may result from a mixture of populations. 'If, however, at least with a great number of elements, the state of affairs appears to be such that the frequency curves hardly differ appreciably from the normal shape this is by no means due to a small number of types in the statistical subjects but appears to depend rather upon the fact that the number of such types is very large' (Charlier, 1931).

Haemoglobin method

In the neonatal period another method can be used to differentiate between blood of the recipient and donor, i.e. the quantitative estimation of alkali resistant and alkali labile haemoglobin. Since Koerber's discovery of differences in the alkali resistance of the haemoglobin of various animals and its confirmation by Krüger (1925) a number of

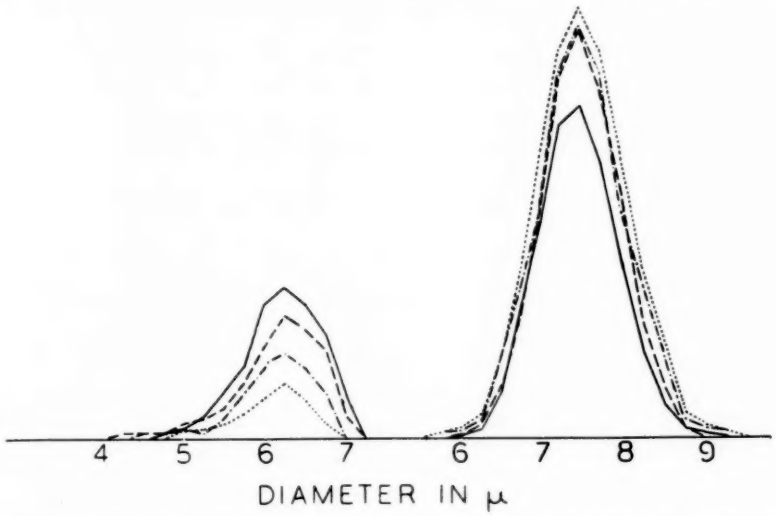

CHART X.—Changes in the major and minor component of the R.B.C. population following transfusion of microspherocytic blood into a normal recipient. The curves result from a decomposition of Price Jones' curves constructed in two-day intervals in the following order: solid curve, dashed curve, dashed and dotted curve, dotted curve.

All these experiments showing the short duration of life of normal R.B.C. transfused into a case of acholuric jaundice and the rapid destruction of red cells from acholuric jaundice transfused into a normal recipient afford support for the opinion (Baar, 1928) that whilst a hereditary defect of R.B.C. in acholuric family jaundice is undoubtedly the main feature of the disease, at least in some cases, some abnormality in the mechanism of blood destruction (spleen) must be assumed.

Decomposition of Price Jones' curves in cases of icterus gravis neonatorum after blood transfusions is usually less satisfactory than in acholuric jaundice. The difference in the mean diameter between the

investigations have been published on this subject. A considerable difference between the resistant foetal and labile adult haemoglobin, first discovered in human blood, has also been found in goats, cattle and rabbits (Barcroft, 1933, 1935; Brinkman and Jonxis, 1936). Krüger's hypothesis, that, the prosthetic group being the same in all haemoglobin, the variability in resistance to alkali is due to difference in the globin component, is now generally accepted.

Credit for the introduction of a spectrophotometric method for following the denaturation of oxyhaemoglobin by alkali is due to Haurowitz (1929, 1930). This method permits quantitative estimation of the process and of the relative amounts of resistant

and labile haemoglobin in a mixture of the two, and allows study of the kinetics of the reaction. It has, however, the disadvantage of depending on a visual comparison and requires a very expensive apparatus. The photoelectric method of Brinkman, et al. (1933, 1935, 1936) has other drawbacks which will be discussed in a later communication. In our experiments we have adapted the method of Haurowitz to use with the Evelyn photo-electric step-photometer (Baar and Hickmans, 1941).

Method. After accurate estimation of the haemoglobin in the blood sample to be examined a 0·12 per cent. haemoglobin solution is prepared in distilled water. The solution is centrifuged and the supernatant fluid poured into another tube, and shaken to ensure complete oxygen saturation. 1 c.c. of the clear solution is placed in each of two cups of Evelyn's microapparatus. 0·2 c.c. of distilled water is added to one cup thus making the solution 0·1 per cent. The extinction (L) * of this solution is determined using filter 540M; this should not differ much from 0·676, the extinction of an oxyhaemoglobin solution of exactly 0·1 per cent. in the spectral region of filter 540M at 1 cm. depth. This cup is now replaced by the other, 0·2 c.c. of a N/4 NaOH solution is quickly added, stirred with a glass rod and half a minute after the addition of NaOH the first reading is taken. Further readings are taken after 1, 1½, 2, 2½, 3, 4, 6, 8, 10, 15 and 30 minutes. When the denaturation of an accurate 0·1 per cent. oxyhaemoglobin solution is complete the extinction of the resulting compound (alkaline globin-haematin) is 0·395. As oxyhaemoglobin and alkaline globin-haematin both follow the Beer-Lambert law the oxyhaemoglobin solution need not be exactly 0·1 per cent. All readings can easily be calculated for an accurate 0·1 per cent. solution. The drop in the extinction $(L^{1\text{ cm.}}_{540\text{ M.}})$ from 0·676 to 0·395 corresponds to 100 per cent. denaturation of a 0·1 per cent. oxyhaemoglobin solution at 1 cm. depth. The difference between these two figures is 0·281. If the extinction at any known time is calculated for an exact 0·1 per cent. solution and this figure subtracted from 0·676 the resulting difference, expressed as a percentage of 0·281, gives the percentage of denaturated oxyhaemoglobin at that time. For example if the extinction of an approximate 0·1 per cent. solution of oxyhaemoglobin is 0·695 and after five minutes denaturation 0·520 the corresponding values for an accurate 0·1 per cent., solution would be 0·676 and 0·505 respectively. The difference between these two figures is 0·171 which is 60·8 per cent. of 0·281; 60·8 per cent. of the oxyhaemoglobin has therefore been denaturated in five minutes.

For graphic representation the procedure of Brinkman and his collaborators is more correct than that of Haurowitz. The logarithms of the haemoglobin concentrations expressed in percentage of the original concentration are plotted against the time in minutes. In the case of a mixture of labile and resistant oxyhaemoglobin the points follow a straight line for a short time and then turn fairly sharply to another straight line with a much milder slope than the first. A typical curve is seen in chart XI. The first linear slope corresponds to the rapid denaturation of labile haemoglobin, the second to the slow denaturation of resistant O_2.Hb. If this second linear part of the curve be extrapolated to zero time the antilogarithm of the corresponding ordinate gives the percentage of resistant oxyhaemoglobin in the specimen examined. The mean error of the method has been determined by making a series of denaturation curves in duplicate, taking the amount of denaturated oxyhaemoglobin after two minutes in each determination and calculating on the basis of the formula $e = \sqrt{\frac{\Sigma d^2}{2n}}$, where e is the mean error, d the difference between duplicates and n the number of estimations. The error so calculated was 2·3 per cent.

In the neonatal period blood is always a mixture of resistant and labile haemoglobin. The amount of labile haemoglobin varies considerably but

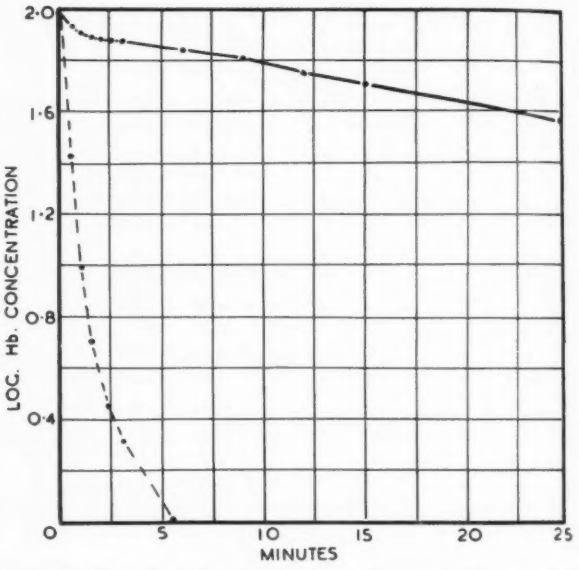

CHART XI.—Denaturation of oxyhaemoglobin in N/4 NaOH. ——— Baby B., age 4 weeks, – – – normal adult. The initial haemoglobin concentration (0·1 per cent.) is taken as 100.

changes slowly in any individual if no transfusion is given, even in cases with a high rate of blood destruction and regeneration.

Chart XII shows the change in the denaturation curve following blood transfusion in a baby with icterus gravis neonatorum. The amount of labile oxyhaemoglobin rose in this case from 52 per cent. before to 74·2 per cent. after transfusion.

The spontaneous replacement of resistant haemoglobin by the labile form takes place slowly but must not be neglected if the fate of transfused cells is to be followed for several weeks. The rate of change, however, shows considerable individual variations. The method therefore is impracticable for observations over a long time and gives an accurate account of the fate of transfused cells only if considerable change in the relation of resistant and labile haemoglobin is produced by transfusion.

Serial determinations of the denaturation curve in twelve cases of icterus gravis neonatorum and erythronoclastic anaemia of the newborn after blood transfusions showed two types of reaction. The first is represented by charts XIII and XIV. The amount of labile haemoglobin increased immediately after

* L corresponds to E in the usual nomenclature of spectrophotometry.

transfusion but thereafter remained almost unchanged for a considerable time. The curves in chart XIII indicate a decrease in the percentage of labile haemoglobin from 89 to 83·4 per cent. within thirteen days; but as in this period there was a spontaneous rise in haemoglobin from 11 to 12·3 a life span of about ten days as calculated from the number of reticulocytes and their maturation time.

The denaturation curves in chart XIV indicate an almost unchanged relation of alkali resistant and alkali labile haemoglobin in the time from 15/6/1940 to 2/7/1940. There was, however, a drop in total

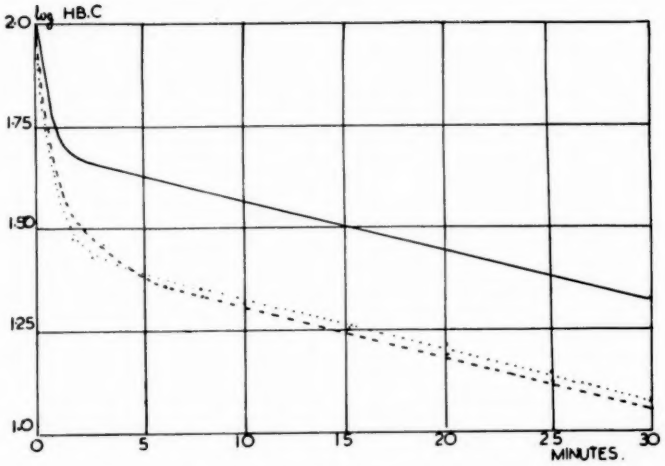

CHART XII.—Denaturation curves in a case of icterus gravis neonatorum, ———— before transfusion (52 per cent. alkali labile oxyhaemoglobin) – – – – – 1½ hours after blood transfusion (72·4 per cent. labile oxyhaemoglobin) and . . . . . 18 hours after transfusion (74·2 per cent. oxyhaemoglobin).

gm. per cent. the absolute figures are 9·61 and 10·2 gm. per cent. The slight increase corresponds exactly to the percentage of labile haemoglobin in the baby's own blood. There was in this case therefore no noticeable destruction of transfused cells within thirteen days. The baby's own cells had haemoglobin from 14·2 to 10·4 gm. per cent. The additional labile haemoglobin was diminished from 5·6 to 3·6 gm. per cent. in seventeen days, which would correspond to a survival of 68 days if the rate of disappearance be linear. The baby had in this period an average of 3·4 per cent. reticulocytes which

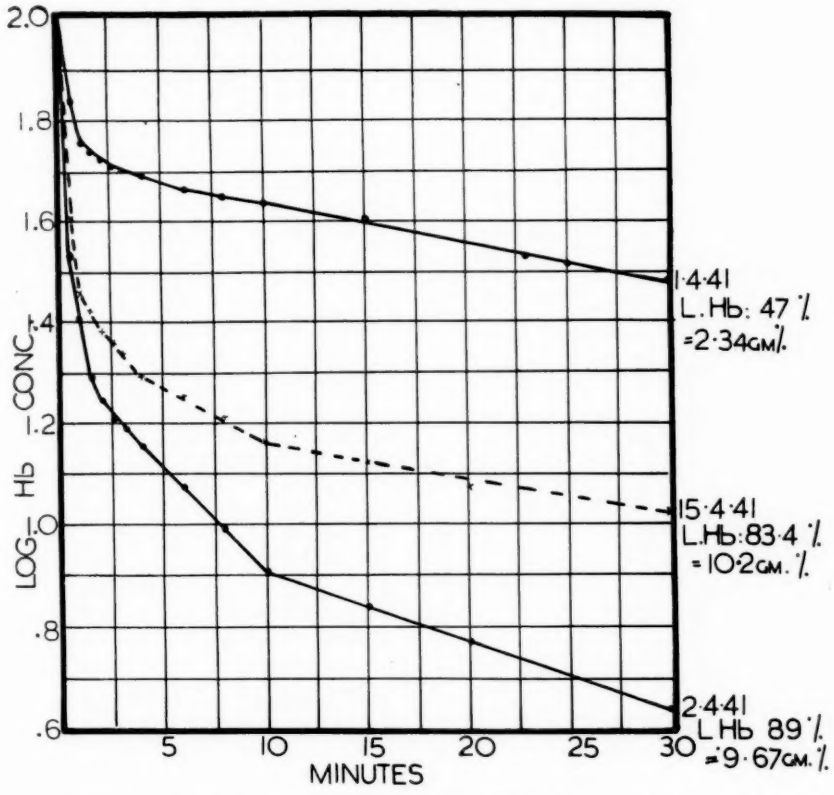

CHART XIII.—Denaturation curves of oxyhaemoglobin in a case of erythronoclastic anaemia of the newborn, before transfusion, immediately and 13 days after blood transfusion. L.HC=alkali labile haemoglobin.

corresponds to a life span of twelve to thirteen days for his own R.B.C.

The second type is represented by charts XV and XVI. In chart XV the oxyhaemoglobin denaturation curves of a baby with acute erythronoclastic anaemia of the newborn are seen. The solid curve before transfusion (2/7/40) corresponds to a mixture of 55·35 per cent. labile and 44·65 per cent. resistant

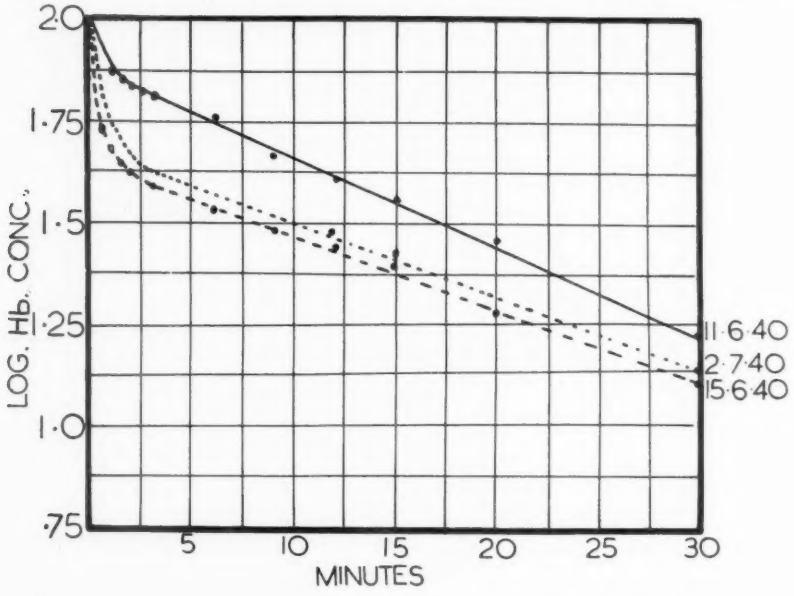

CHART XIV.—Denaturation curves of oxyhaemoglobin in a case of icterus gravis neonatorum before transfusion, immediately after transfusion and 17 days later.

oxyhaemoglobin. The second solid curve (3/7/40) was made immediately after blood transfusion. This shows 77·09 per cent. labile and 22·91 per cent. resistant haemoglobin. Forty-eight hours later the denaturation curve indicates 56·35 per cent. labile and 43·65 per cent. resistant haemoglobin, almost the same as before transfusion ; the transfused cells, therefore, must have disappeared within two days. The life span of the baby's own cells, which in cases where the haemoglobin level is unsteady can only be roughly estimated from the number of reticulocytes and their maturation time, was about two days. It is apparent that in this case destruction of the red cells was taking place irrespective of their age and quality. Cases with such indiscriminate destruction of R.B.C. of which two have been seen had all the haematological signs of a severe haemolytic process (charts XV and XVI).

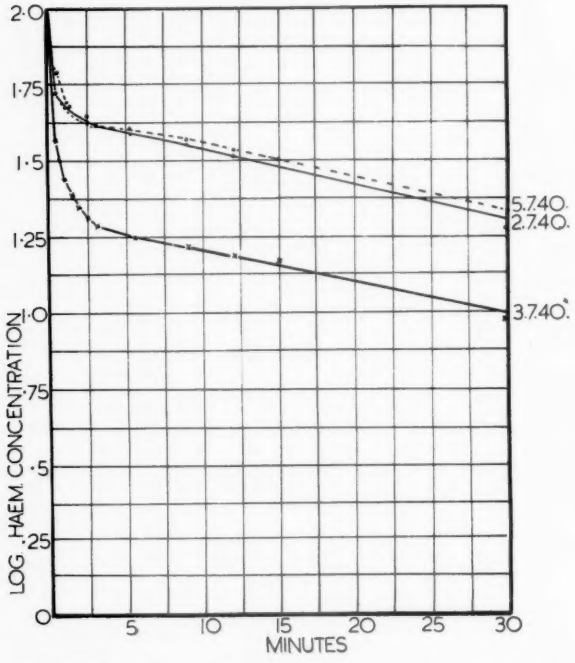

CHART XV.—Baby Pr. Alkali denaturation of oxyhaemoglobin before and after blood transfusion.

These observations throw some light on the pathogenesis of icterus gravis neonatorum and erythronoclastic anaemia of the newborn. Cases with indiscriminate destruction of the cells both of donor and recipient within so short a time as two days afford incontestable proof of the presence of an 'haemolytic' * process and confirm the thesis put forward by Parsons and his school (1933, 1935, 1938). On the other hand cases in which the abnormal destruction is largely confined to the patient's own cells suggest that these may be of inferior quality. We have, however, encountered several cases of intermediate type of R.B.C. destruction which serve to link the two extreme types already described and it seems probable therefore that the agent which causes violent haemolysis in some cases may in others chiefly cause injury to the bone marrow and result in the production of erythrocytes of inferior quality. The anaemia being in fact rather erythronoclastic than haemolytic in origin.

It will be seen that it has been possible by both decomposition of Price Jones' curves and esti-

* 'Haemolytic' is used here in the widest sense of the word meaning a rapid destruction of R.B.C. whether this is due to a circulating poison, to a haemolysin, or to a pathological function of tissue normally concerned with the destruction of erythrocytes.

mations of alkali resistant and alkali labile haemoglobin to demonstrate cases in which there was selective destruction of the red cells either of the recipient or donor. Review of the literature reveals several observations which can only be interpreted in the same way. As early as 1857 Brown-Séquard showed that the red cells of a fowl when transfused into a dog or rabbit disappeared within an hour, while those of dog or rabbit survived in the fowl's circulation for a month. In Ashby's experiments also the number of transfused erythrocytes often remained unchanged for weeks though there can be

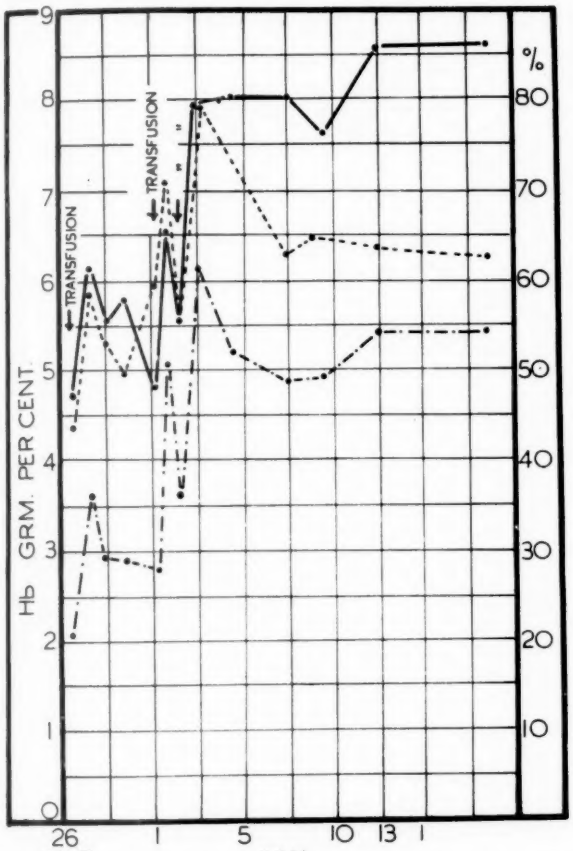

CHART XVI.—Baby Pr. ———— gm. per cent. haemoglobin in the peripheral blood, – – – – – gm. per cent. alkali labile haemoglobin, –.–.– alkali labile haemoglobin in per cent. of total haemoglobin.

no question but that some of the recipient's own cells were destroyed and replaced during this period. In one instance quoted in part XII two transfusions of group O blood were given to a patient with pernicious anaemia after a transfusion with group A blood, the recipient being also group A. Seventeen days after the transfusion of group A and twenty-four hours after the second group O transfusion the only cells demonstrable in the recipient's circulation were not agglutinable, that is to say all R.B.C. of the recipient and of the group A donor had been destroyed leaving only those of the group O donor. This phenomenon is comparable with that in the case of erythronoclastic anaemia described on p. 125 when Price Jones' curves revealed the complete replacement of the recipient's R.B.C. by those of the donor.

In most observations of selective cell destruction in which the course of events could be followed for a sufficient length of time the transfused cells outlived those of the recipient. The chief exceptions were those cases in which abnormal blood, that is blood from cases of alcholuric jaundice, was given to normal persons. In almost all instances although the donor's R.B.C. had a longer life span than those of the recipient they did not survive so long as does the average red cell in normal persons. Observations such as that in chart XIII and XIV in which the amount of alkali labile haemoglobin remained unchanged for thirteen days or a life span of 68 days was calculated for the transfused cells suggest the possibility that selective destruction of the recipient's cells may even lead to a prolongation of the life span of the transfused cells beyond the normal. It has been pointed out above, however, that this method is susceptible to some error if observations are continued over long periods and have therefore no certainty about this point. All our studies have been made on cases of haemolytic anaemia. If under these conditions indications of such abnormal survival of transfused cells are detectable it seems probable that this will be far more frequent if the recipient is not subject to a haemolytic condition; this suggestion finds some confirmation in the findings of Ashby and others.

It has been shown above that the conception of an 'intrinsic' longevity of the red cell is purely relative, depending as it does entirely upon environmental circumstances. Transfused cells may disappear from the circulation at a regular rate, indicating that the principal cause of death is old age, yet their life span may be much diminished. The life span of erythrocytes is determined by three factors, the intrinsic properties of the red cell, the activity of the blood destroying mechanism which may include the presence of an haemolytic poison, and in the case of transfusion the adaptation of this mechanism to the transfused cells. The first factor is proven by observations of the destruction of transfused cells at a different rate from the recipient's cells. The second is made clear by the shortening of the red cell's life span when transfused to cases of haemolytic anaemia. For the third factor we have no evidence in our own investigations but it is strongly suggested by the observation of Ashby in which both the cells of the recipient and one donor were destroyed and only those of group O survived.

Analysis of the fate of transfused erythrocytes by two different methods applied for the first time to this problem and comparison with the results of differential agglutination tests reported in the literature shows the action of various factors on the time for which transfused cells survive in the recipient's circulation. Indiscriminate destruction, selective destruction of the cells of the recipient or donor and shortening of the life span of transfused cells have been demonstrated and it seems probable that the life span of such cells may in some cases actually be

prolonged. Transfusion experiments, therefore, give valuable information about what Josephs (1932, 1934) calls the 'mechanism of anaemias', but are useless for the estimation of the normal life span of the erythrocyte.

Summary

1. The fate of transfused red blood corpuscles has been followed by decomposition of Price Jones' curves and by quantitative estimation of alkali-resistant and alkali-labile oxyhaemoglobin. A method for the latter estimation with the use of Evelyn's photoelectric step-photometer is described.

2. The life span of transfused cells is usually different from that of the recipient's cells. The disappearance of transfused cells, both as the result of old age and of indiscriminate destruction, have been demonstrated. A diminution in the average life span is usual, but prolongation may occur.

3. Transfusion experiments have demonstrated the inferior quality of erythrocytes and the increased activity of the destructive mechanism in acholuric jaundice and the presence of an erythronoclastic factor in icterus gravis neonatorum and haemolytic anaemia of the newborn.

4. No conclusions as to the normal life span of erythrocytes may justifiably be drawn from transfusion experiments.

Grateful thanks must be expressed to Professor L. G. Parsons for the interest with which he has followed these investigations and for his criticism and suggestions, to the Honorary Staff of The Children's Hospital, Birmingham, for access to their cases, to Miss Finch, M.Sc., assistant biochemist, for potassium determinations, to Mr. Brain for the photographs and charts and to the Board of the Children's Hospital for a personal grant to one of us (H.S.B.).

The investigations reported in this article were completed early in 1941. The recent discoveries concerning the rôle of anti-Rh agglutinins in the blood destruction in icterus gravis neonatorum could, therefore, not have been taken into consideration. A few quantitative estimations of alkali resistant and alkali labile haemoglobin after transfusions of Rh-negative blood, made in the past months, suggest a selective destruction of baby's cells. This is in agreement with the results obtained by Mollison with the Ashby method.

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(For parts xii, xiii, and xiv)

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HEAD INJURIES IN CHILDREN

AND THEIR AFTER-EFFECTS

BY

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Children form a considerable proportion of admissions to an accident service. The proportion of fatal road accidents was 1,049 children (under fifteen years of age) to 8,347 adults during the first year of the war, and 1,494 to 10,077 during the second. In non-fatal road accidents, the proportion of children to adults is slightly higher—approximately 1 to 5:

October, 1941, 2,826 children to 14,824 adults.
October, 1942, 2,097 children to 11,121 adults (Safety News, 1942).

The material for this study is taken from a series of 320 head injuries admitted between July 1, 1941 and June 30, 1942. Among these were fifty-eight children (under fifteen years of age), including only one fatal case. To this were added two cases admitted immediately before, thus bringing the consecutive series up to sixty. In addition, six earlier cases were included, seen on account of their severity.

The admissions were not evenly distributed over the year; the figures were:

July–September	19
October–December	7
January–March	10
April–June..	22
	58

The difference between the figure for the summer half-year (April–September: 41) and the winter half-year (October–March: 17) is statistically significant. It is known that few children are killed after dark. So it would appear that the higher frequency of head injuries in summer is due to the longer daylight hours; they mean more opportunity for play in the open, and therefore a greater risk of exposure. This is true not only of road accidents, but also for accidents in play-grounds and at home.

Fatal road accidents are much more frequent in children between three and eight than in older children. There was no such difference of age incidence in the non-fatal cases (thirty-three cases under eight, thirty-three cases eight or over). The numbers are slightly lower in the lowest quinquennium (eighteen) than in the middle (twenty-three) and upper (twenty-five).

There was a marked difference in the sexes (forty-five male to twenty-one female).

Causation. The sixty cases of the consecutive series were distributed as follows:

ROAD ACCIDENTS:	41		
		Pedestrians	15
		Cyclists in collision ..	7
		Cyclists, no other vehicle involved	7
		Passengers in vehicles ..	11
		Hanging on van.. ..	1
			41
AT PLAY:	19		
		At home	5
		Outdoors	13*
		Unclassified	1
	60		19

Some details not given in the table are of interest. The majority of the pedestrians were legitimate road users, children going to school or on errands. Only two children were playing in the street, and in one other case that suspicion could not be excluded. One or two small children slipped from their mother's hand. In no case was 'darting into the road' (a frequent cause of fatal accidents) admitted, though the account from the other side might have been different. The vehicles involved were cars (seven), lorries (four), motor cycles (three) and omnibus (one).

Of the injured 'passengers' only four were involved in collisions (two cars, one motor cycle and one bicycle, the child riding on the handlebars). Of the remaining seven, five were children of three and four years, falling from a running car. In all instances their parents were with them, but failed to prevent them from opening the doors or climbing over them. The two others were unaccompanied children of six, falling from a moving bus.

Personal accident liability. It was thought that dull or defective children might be particularly liable to be injured owing to carelessness or failure to grasp the road situation and to respond to danger quickly and sensibly. Therefore data about the intelligence of the patients were collected. The results are given

* The number includes one certain and one doubtful case of petit mal attack, accounting for the accident.

in the table below. Estimates were not only based on the observation in hospital, but on school attainments and school reports. Tests used were either Binet (Terman-Merrill) or Raven's Matrices, and in some cases Kohs Blocks Designs and the Good-enough scale in addition. The figures refer only to children of school age.

TABLE 1

Tested	I.Q. below 90 under 25 percentile 4	I.Q. 90–110 25–75 percentile 7	I.Q. above 110 above 75 percentile 9	Total 20
Estimated	Below average 3	Average 14	above average 1	18
Total ..	7	21	10	38

These figures do not bear out the original assumption, showing as they do a fairly normal distribution of intelligence.

Repeated accidents may be an indication of personal accident proneness. Five of the patients had previous head injuries, two had had injuries to other parts of their body (one patient appears in both groups). Only accidents which the mothers regarded as such were counted, i.e. not ordinary falls, and the figure can therefore be regarded as high, considering the age group and the figures in adults. However, no comparable material for children is available, and no definite conclusions can be drawn.

Clinical picture

(1) FRACTURES. The impression has often been recorded that the skull of the child is more liable to fracture than that of the grown-up. This is somewhat surprising considering the elasticity of the bones of children; but no comparative figures are available. In this series the incidence of fracture was as follows:

Closed fissured fractures	17	Negative x-rays ..	28
Depressed, not compound	1	Fractured nose only ..	1
Compound	6	Dead	1
Involving sinus ..	1	No x-rays taken ..	4
Clinical evidence of fractured base (aerocele)	1		
	26		34

This incidence is compared with that in 165 consecutive adult admissions in table 2.

TABLE 2
FRACTURES

	Total	Fractures	Percentage	Standard error
Adult	165	45	27·2	3·086
Children ..	60	26	43·3	6·389
Difference ..	—	—	16·1	7·10

This difference is statistically significant, being 2·26 times its standard error.

(2) NEUROLOGICAL SIGNS. Twenty-seven out of the total of sixty-six cases showed definite neurological signs. This figure, however, gives no accurate picture, because the incidence of neurological signs depends to a large extent on the interval between the injury and the first examination. Seen immediately after concussion, most children are liable to show bilateral extensor plantar responses which tend to disappear quickly with the recovery of consciousness. Furthermore, children seem to show neck rigidity more readily than adults with comparatively small amounts of blood in the cerebrospinal fluid.

The most striking difference in comparison with adults is the frequency of fits shortly after injury. Among the sixty children of the consecutive series five developed fits within about an hour of the accident, three generalized convulsions, and two Jacksonian fits. Figures for adults, as found in the literature, vary between 5 per cent. and 0·1 per cent., and they are difficult to compare as some writers call 'early' fits within the first week, others within the first month.

In the authors' experience, there was only one early traumatic fit among 165 consecutive adult admissions. This shows that the incidence of early fits is much higher in children.

Early traumatic epilepsy is generally explained by direct cortical irritation; children are known to respond to all sorts of harmful agents by 'symptomatic' convulsions. It is therefore likely that the relative frequency of traumatic fits in children as compared with adults, is due to this general disposition rather than to the type of injury; this observation suggests that there are similar constitutional factors in those few adults who develop fits soon after injuries which in themselves show no conspicuous features of cortical injury such as driven-in bone, to account for this effect.

(3) MENTAL STATE. It is much more difficult in children than in adults to assess unconsciousness, unless it is actually observed. In milder cases in which the patients are alert at the time of admission, it is therefore often open to doubt whether they have been unconscious or not. The post-traumatic amnesia is no reliable guide in smaller children. Definite evidence of unconsciousness, viz. observation in hospital or by reliable witnesses, or amnesia, in suitable cases—was present in thirty-eight cases. The duration of unconsciousness or of the post-traumatic amnesia was:

under 1 hour ..	.. in 23 cases
1 to 24 hours ..	.. ,, 8 ,,
over 24 hours ..	.. ,, 7 ,,

As the standards were not uniform, the distinction between the groups is too vague for any statistical application.

The demonstration of clouded consciousness is still more difficult than the assessment of unconsciousness. During the recovery from unconsciousness children present a different clinical picture from

that seen in adults. Emotional symptoms prevail, and it is impossible to say whether they are the only ones, or whether they mask the intellectual disturbances characteristic of the clouded consciousness in adults.

During this period the children, left to themselves, are quiet and apathetic; when talked to, they turn away. During the physical examination they resist and cry. They are irritable, fretful and morose; they do not respond to the usual little bribes. Now, all sick children tend to behave like this, and this behaviour may be understood as the childish reaction to being sick, perhaps intensified by the sudden awakening in strange surroundings. It is peculiar, however, that this emotional state ends suddenly, as a rule, and this change does not look like the adaptation of the child to new surroundings.

The child wakes up one morning as a 'different child'—very reminiscent of the adult's waking up from a state of clouded consciousness. Time and again when it seemed that the patient was a shy, resentful or stupid youngster, it was surprising to find, a few days later, a nice, cheerful and well-behaved child. Thus it began to be apparent that this emotional state was an equivalent of the adult's clouded consciousness. This syndrome, more or less marked, was present in seventeen out of sixty cases. Blau (1936) has published cases of mental disorder after head injury (in children) so severe that admission to a psychiatric ward was required: the picture he describes could well be regarded as that in the present observations, intensified to an extreme degree. The following is an example from the cases under discussion:

Marjorie B. (R.I. 22040), aged ten years, admitted March 31, 1942. This girl attends a village school a mile and a half away from her parents' house. On the way home she was knocked down by a motor cyclist. Admitted one hour after the accident she was deeply unconscious. She had bilateral compound fractures of tibia and fibula, a lacerated wound on the right side of the forehead, and a compound depressed fracture in the left parieto-occipital region. The legs were operated on the same day; the scalp wounds were excised the following morning. The occipital wound was enlarged, the depressed bone removed, a small hole in the dura stitched and the wound closed in layers without drainage. The patient remained unconscious for a week, though she gradually began to respond to painful stimuli, to swallow fluid, to pull her bedclothes up. On April 10, she appeared awake, but was still mute and did not carry out verbal requests. She resented interference, cried when touched, and for no obvious reasons frequently started screaming. On April 14, she was still disinclined to co-operate at any examination; she threw away a pencil put into her hand, and made no active effort to feed herself. She was very irritable, and burst out screaming at the slightest interference. On April 21 she began to speak to other children and to the nurse who looked after her, but was still irritable, resentful, unco-operative and rude. She tried to get out of bed and to go home, though both her legs were in plaster up to the hip. She snatched another child's dinner, tried to take the doctor's fountain pen and other children's toys. She kept on asking for the same things. Early in May her behaviour changed; she was homesick and cried she wanted to go home. She still had bouts of irritability, but in the intervals she behaved much more normally. Towards the end of May she became nice and polite, and perfectly co-operative at physical examinations and mental tests. The only definite neurological sign she had was a left external rectus weakness (her lower extremities were in plaster all the time). Results of tests, carried out in the last week of May; Binet (Merrill Terman) I.Q. 83; Raven Matrices 25 percentile; reading age (Burt) between 9 and 10 ; arithmetic age 9 ; spelling age 9 ; drawing (Goodenough scale) age 7.

When she was re-examined on September 26, 1942, her mother reported that she behaved perfectly normally at home. She took up lessons at home and made good progress. She was fit now to go back to school (this involves a one-and-a-half mile walk). On examination she showed a slight inequality in knee and ankle jerks on the two sides, otherwise no neurological signs. Her behaviour during the interview was unexceptional. She was co-operative in tests. Her mental age, in Kohs block design test was 9·8 corresponding to an I.Q. of 93.

The Head Teacher of her school reported on December 10, 1942:

> 'Although she was absent from school for nearly seven months, she was on her return able to take up her work where she left off. . . . She has made good progress, and there are no changes in her attitude towards school life, or in her behaviour. The only difference I have noticed is that she is a little more quiet in manner.'

(4) HEADACHE. This has not been mentioned before, because this symptom is of greater importance as an after-effect than in the acute stage. It has often been said that children do not suffer, or suffer less frequently, from headaches than do adults. It seemed worth checking this impression in the present series. Notes on headaches were taken at least at the first thorough examination and on discharge from hospital, and later on at each follow-up visit; in the earlier cases at least three times, in some of the more recent ones only twice. If on any occasion the child reported headache, the case was recorded as positive; the figures are therefore bound to be on the high side. The results were:

	In hospital	After discharge
Positive	16 (35 per cent.)	10 (25 per cent.)
Negative	30	30
Total of statements obtained ..	46	40

The figures during hospital treatment are slightly lower than those for adults, the figures after discharge practically the same. They are, however, not strictly comparable owing to the different procedure in collecting the material. Considering this, it can only be stated that headache as a symptom of the early stage is of comparatively small importance. The significance of persistent headache as an after-effect will be discussed later.

Hospital treatment

The children were not treated with prolonged rest, as even modern text-books still recommend; but they were given the same active rehabilitation, as is the routine in adult cases. They were not kept in the horizontal position, unless they themselves felt like lying flat, and they were encouraged to get up, as soon as their general condition permitted. In a considerable number of cases the duration of in-patient treatment was determined by injuries to other parts of the body. The actual figures, without making allowances for this, were:

Up to 1 week	31
2 weeks ..	18
3 weeks ..	6
4 weeks ..	6
5 weeks ..	1
7 weeks ..	2
12 weeks ..	2
	66

Both the twelve-week cases were kept so long on account of extensive injuries to other parts of their bodies. Excluding them, the average stay is 1·5 ±1·14 weeks. It gives, however, a clearer picture to say that three-quarters of the patients were discharged in under two weeks.

After-effects

Out of the sixty-six cases, twenty were below school age, and four had left school at the time of the accident. Of the forty-two school children, in four cases no exact information about the date of their return to school could be obtained; two were still away from school six months after the accident; one patient died. The remaining thirty-five cases were distributed as follows:

ABSENCE FROM SCHOOL

1 week	4	8 weeks	1
2 weeks	5	9 weeks	1
3 weeks	6	11 weeks	1
4 weeks	4	14 weeks	1
5 weeks	3	15 weeks	1
6 weeks	2	16 weeks	1
7 weeks	5		

In a few cases the absence from school was longer than necessary owing to vacations.

In no case without associated injuries to other parts of the body was it found necessary, as Ford (1937) suggests, to keep the child away from school for six months or more.

The table shows that a quarter of the cases lost two weeks or less: half between two and seven weeks; and a quarter more than seven weeks. No allowance was made in the table for prolonged absence owing to injuries to other parts of the body.

In the 'over-seven-weeks' group were two patients who had had lacerations of the brain with aphasia, one child in poor general health who had attended school irregularly before, a boy who, since he was an evacuee, had to be sent to a convalescent home on discharge from hospital, the other a neurotic girl, Mary J. (see below); the length of absence in the last case was due to the school holidays.

The 'seven-weeks' group included one case of subdural haematoma, one case of compound, depressed and infected fracture, two severe injuries to other parts of the body, and one neurotic girl.

Regarding two to seven weeks of absence from school as the 'normal' time according to the table, four to five weeks can be considered as a reasonable maximum in cases without special complications.

Late signs and symptoms. The impression gained from the literature about frequency and severity of after-effects is necessarily biassed, as severe and unusual results are more likely to be published than ordinary cases. Starting from surgical material (of which however not more than half could be followed up) Stone and Brams (1927) found headache in 20 per cent. of the cases, Beckman (1928) who made a very thorough follow-up study of a large and unselected group found some after-effects in 23 per cent. of the cases, but only in a very few of these (less than 5 per cent.) were the symptoms permanent.

In the present consecutive series of sixty cases seventeen patients (or their mothers for them) complained of nervous or mental after-effects at some time after discharge from hospital; so did two out of the six earlier cases which made up the series.

Several syndromes can be distinguished among the after-effects:

(a) POST-CONCUSSIONAL SYNDROME. Six patients complained of headache and/or giddiness. All these except one, were thirteen or fourteen years of age. The sixth case, a boy of nine (Donald B. R.I. 17644) after a previous head injury treated elsewhere, developed petit mal attacks which he described as sensations in his head. The accidents of all the children in this group were comparatively mild, and all cases showed psychological or social features which seemed adequate to account for the continuation of the symptoms. In other words, children of this age behave similarly to adults, but the picture is more coloured by the influence of home environment. The following case is an example:

Mary J. (R.I. 22509), age twelve years, admitted April 25, 1942, after colliding with a lorry while cycling. She was unconscious for a few minutes, but recovered consciousness on admission. Her post-traumatic amnesia was about thirty minutes. She had a few bruises in the face, on the shoulders and knees, no bleeding from nose or ears, no neurological signs. X-rays showed a fissured fracture in the left temporal region. She complained of no headache, nausea or vomiting. During the next few days she complained of some headaches and some giddiness, when first getting up. She also developed some pain in her right ear, in obvious imitation of another girl in the next bed, who had been involved in the same accident, and had had a fracture through her left mastoid process with bleeding and deafness. With some suggestion and the usual active management she improved and was discharged free from symptoms on May 11, 1942.

When seen again on July 25, 1942, she complained of headache, poor sleep and failing concentration. She had returned to school a fortnight before this consultation, but she started vomiting and feeling unwell, so arrangements had been made for her to have breakfast in bed, get up at ten, and attend school in the afternoon only. On examination she looked a perfectly healthy child. She was over-carefully dressed, very ladylike and artificial in her behaviour. Her hair was elaborately curled (done every morning by her mother who commented—'The only thing I can do for my child'). The neurological examination was entirely negative, and the child's description of her complaints was vague and inconsistent. The mother regards her as a martyr and an invalid, although she herself points out how unreliable the child's statements are. The family doctor thinks the concentration required at school is too much for the child and told her so: the mother repudiates the suggestion that the patient's recovery could be comparable to that of other children; she is so sensitive and highly strung that she could not be expected to recover in the normal time.

The mother herself is a highly-strung, over-anxious woman. She had the main responsibility for her children's early up-bringing as her husband was at sea.

Patient is the younger of two children. She is described as unusually artistic, and she has had dancing lessons since the age of three. She has raised 'hundreds of pounds' for charity by her public appearances. As long as she went to Junior School, she was taken in the bus by her mother four times a day and was not allowed to mix with the 'rough' children in the neighbourhood. She was teased a lot as 'Shirley Temple.' She had suffered from bilious attacks and colitis, had had her tonsils out and some operation on her ear. She has been subjected to several medical examinations for an insurance company since the accident, and the claim has not been settled yet (December, 1942).

(b) NEUROTIC SYNDROMES. One boy, a defective, developed an hysterical limp. Three children developed nightmares or fear of the dark; two of them were described as highly strung before, though nightmares were not mentioned in their previous histories.

In one pre-pubescent boy who had nightmares only when sleeping in the same room with his elder sister, the psychogenesis was fairly obvious; in the other cases there is not much reason to assume that the physical injury in itself had much to do with the symptom. The fact of having had an accident, and perhaps maternal over-concern, are probably sufficient explanation. The same considerations are valid in two cases in which mothers complained of fidgetiness in children, who admittedly had been fidgety before.

(c) EMOTIONAL SYMPTOMS are most difficult to assess. Irritability was complained of in six cases. Three of the six were small children between three and four. Irritability, fretfulness and difficulty in managing them were the only symptoms the mothers noticed, and nothing was found on examination.

A boy of six had had cerebral laceration with aphasia, and he had had headache at the same time. A girl of twelve had had an extradural haemorrhage; she was a pleasant, well-adjusted child, well observed and sensibly managed by her mother who noticed her slight irritability as the only symptom.

This was a case in which there could be little doubt about the organic origin of the symptoms, slight as the disturbance was.

A boy of twelve was very different. He was found in the road in a semi-conscious state; the circumstances of the accident were never quite clear, as everybody tried to hush them up. A strange bicycle was found near the site of the accident, and it was suspected that the boy had 'borrowed' it, though he professed complete amnesia and wondered whether somebody had knocked him out. His irritability manifested itself only in quarrels with his mother who thought that he complained of morning headache only in order to get his breakfast in bed. He also wanted to have his roller skates which she took away from him, as she thought that they were too dangerous. The boy had never had any neurological signs, no fracture of the skull, and only a small haematoma in the occipital region, and the retrospective history showed him to be a highly-strung boy, whom the mother indulged and scolded by turns.

It would seem, in the light of the last case, that irritability and other emotional symptoms require closer analysis before they can be regarded as the result of cerebral injury; the severity of the injury, the neurological signs, the patient's age and disposition and the social and psychological setting in which the symptoms occur, all have to be taken into account before any definite conclusion can be drawn. The separation from home, and the return after some absence, may bring into play psychological factors, the importance of which is seen in Child Guidance cases. It seems justifiable to say that in children in the late as well as in the early stage after injury emotional symptoms are a more common and a more characteristic sign of disturbed cerebral function than is intellectual loss.

(d) CHANGE OF CONDUCT. The most serious after-effect of cerebral injury in childhood is a change of conduct, a behaviour disorder, often described as 'change of personality' or 'deterioration' of character. Strecker and Ebaugh (1924) have drawn attention to this clinical picture which is similar to the mental changes described in the late stages of epidemic encephalitis. The main features are over-activity, restlessness, impulsiveness, cruelty, emotional instability, temper tantrums, truancy, delinquency. Kasanin (1929) and later Blau (1936) have described such cases. The condition is obviously rare, and much criticism has to be applied to the evidence in cases seen at long intervals after the injury, before one can accept the traumatic aetiology of the condition. This is particularly true in court cases, but in ordinary hospital practice allowance must be made for the general tendency to ascribe to falls or head injuries all sorts of ailments and defects of intellect or character.

In this series there were only two cases where the question of traumatic behaviour disorder had to be seriously considered, one a court case and the other a case of wetting and soiling. It may be worth quoting the histories in brief:

Case 1. John H. (R.I. 17553), aged thirteen years, admitted August 23, 1941, after having been knocked down by a car. He had a laceration of his forehead, but no fracture of the skull; he was conscious on admission, and his traumatic amnesia was a few minutes only. The neurological examination was negative. He recovered very quickly; his behaviour in the ward during the six days he was an in-patient was somewhat different from that of other children; he was lively, talked to everybody, shouted across the ward. In the subsequent months he had a short period of headache, and also complained of sleepiness, but this was probably due to luminal which he was given for a period.

In January, 1942, he ran away from home once; he stayed away for five days, and was finally found by the police, camping in an empty house.

In February, 1942, his mother complained for the first time about his outbursts of temper.

In May he was brought before the Juvenile Court. In the absence of his parents he had taken 10s. and had gone off, hitch-hiking to Reading. There he was found sleeping in somebody's car and was handed over to the police.

His behaviour disorder was thought to be due to the injury.

It appeared, however, that something similar had happened before his accident. He had stolen a bag out of a car; he was going with a ' gang ' of other boys, about whose activities no more details could be obtained.

A cursory examination showed some factors to account for his behaviour.

His father was away in the Army, and his mother did not find the right approach to him. Though highly intelligent and a first-class scholar, he disliked school, and wanted to be a farmer. He had become dissatisfied since plans for him to go to Canada had not materialized. Circumstances prevented a fuller elucidation of the involved emotional situation.

Case 2. Stanley S. (R.I. 17061), aged eleven years, admitted July 31, 1941, following a road accident; he was hanging on a milk van, which backed unexpectedly and he fell off. He was conscious on admission, but had amnesia for a few minutes after the accident. He had a right external rectus palsy, and was bleeding from his right ear. X-rays showed a small amount of air in his middle fossa, but did not demonstrate the fracture of the base which must have been present. Within the next two days he developed signs of meningeal irritation, with 300 white cells in the cerebrospinal fluid. He was rather drowsy for a week, but he recovered with sulphanilamide treatment. He was fit for discharge to a convalescent home three weeks after the injury, the only remaining sign being the oculomotor palsy.

He is one of five children; prior to the War he had been in a home on account of undernourishment. He was billeted with a decent woman who prided herself on her ' way with boys ' and who made it her job to win his affection. Though she described him as a nice, willing and sociable boy, it did not surprise her that he did not get on so well with the nurses in hospital. Three weeks after the boy's return to her, she complained to the billeting officer that ' he was not the boy he used to be.' She found him sullen and unresponsive and not so willing as formerly to do things for her. He forgot things on an errand, and there was some quarrel because she did not want him to go on a lorry with other boys for potato-picking. There were many indications that she was treating the boy as an invalid which he much resented.

He returned to school where his attainments were as good as before.

There was no complaint about his behaviour there, but his foster-mother reported in January, 1942, that he had soiled and wet the bed at night. More detailed inquiry showed, however, that the boy had visited his own home, and had brought back extra pocket money, most of which he had spent on ice-cream. On another occasion, having had his usual tea he had gone to a Sunday School tea party, and on return had been sick, as also was the other evacuee in the household.

Further inquiry six months later confirmed the opinion that the symptoms which were complained of by the foster mother were of a temporary nature only, and were not in any sense attributable to the injury as such.

(e) INTELLECTUAL SYMPTOMS. Deterioration of intelligence or disturbance of intellectual development are the most serious after-effects of cerebral injury one might anticipate in children. To supplement the follow-up examinations it seemed, therefore, important to follow the children's school career subsequent to their accidents. School reports were available in thirty-five cases. In all cases of serious injury or doubtful outcome contact was made with the teacher personally by letter or visit. In thirty-two cases the reports stated definitely that the children's performance had not fallen off; in two defective children the results could not be accurately assessed. In one case only did the comparison of school reports before and after the accident show a definite deterioration in school performance. This was the case Donald B. (vide, p. 142) who suffered from traumatic epilepsy, the deteriorating effect of which on intelligence is well known.

Summary

Sixty cases of head injury in children are reported. The incidence was higher in summer than in winter. Boys were more numerous than girls. Two-thirds of the cases were due to road accidents. The intelligence of the children was average and did not give any indication of their accident liability. Fractures of the skull were more frequent than among adults. In the acute stage emotional symptoms were more impressive than clouded consciousness and intellectual loss. The incidence of headache did not differ much from that in adults. Two-thirds of the cases were fit for discharge after two weeks' treatment in hospital. The absence from school due to the accidents was two to seven weeks

in half of the cases, in one-quarter less, in one-quarter more. The post-concussional syndrome was observed in 10 per cent. of the cases; its incidence depended to a large extent on environmental factors. Irritability was the most common after-effect. Persistent behaviour disorder was rare in this series, as also was intellectual impairment.

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FIBRINOGEN DEFICIENCY AS A FACTOR IN HAEMORRHAGIC DISEASE

BY

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Three local factors are concerned with arrest of haemorrhage. Magnus (1924) was the first to describe the contraction of the capillaries following injury and considered this to be the initial stage in the arrest of haemorrhage. Secondly, platelets are deposited on the damaged areas of capillary endothelium where they act as protective agents, forming a platelet thrombus, which, however, does not form a firm clot. This is seen in haemophilia where, in spite of a normal bleeding time, gentle squeezing causes renewed bleeding even after some hours (Frank, 1925; Baar, 1928). Finally, thrombokinase is liberated from disintegrated platelets and damaged tissue cells and in the presence of calcium converts prothrombin to thrombin, which in turn interacts with the fibrinogen of the plasma to form fibrin. Thus a firm thrombus is formed and the capillaries are efficiently occluded.

These factors are on the one hand interdependent, e.g. the agglutination of platelets, their disintegration and liberation of thrombokinase; on the other hand there can be, as has been pointed out by one of us (Baar, 1934), a compensation of one deficient factor by another. This can best be seen from the experiments of Roskam (1921), who produced by intravenous gelatin injections either a reduction of platelets, an incoagulability of blood or both together. The bleeding time was moderately prolonged in the first instance, normal in the second, but very considerably prolonged in the third.

At various times one or other of these factors has been the focus of attention. Recently the prothrombin content of the plasma has been in the foreground, particularly with regard to the haemorrhagic diathesis, and has tended to overshadow other factors so that haemorrhagic disease of the newborn is often considered to be synonymous with prothrombin deficiency. Although prothrombin deficiency (quantitative or qualitative) without doubt is present in haemorrhagic disease of the newborn, the mechanism of the haemorrhage is not so simple as it would appear from recent papers.

From time to time cases have been reported in which a haemorrhagic tendency was associated with a complete failure of the blood to clot and a reduction or absence of blood fibrinogen.

Review of the literature

The first case was described by Rabe and Salomon (1920) and was followed up four years later by Breckoff (1924). The patient, a boy aged thirteen in 1924 had bled periodically into the skin and had bruised easily since birth. During the symptomatic phases the bleeding time was raised to at least forty-eight hours, but was reduced to five minutes following blood transfusion. The blood, however, never clotted in vitro and at no time was fibrinogen detected in the blood. To explain the periodicity of symptoms an unknown alteration in the vessels was postulated as the other factor necessary for haemorrhage.

Opitz and Frei (1921) then reported a fatal case in an eight-month-old female infant who had had haemorrhage from the stomach and bowel since birth. No factor inhibiting blood coagulation could be demonstrated and in addition to the absence of fibrinogen the platelets were reduced to 114,000 per c.mm.

In both the above cases the haemorrhagic tendency had dated from birth. Opitz and Silberberg (1924) now described a fatal case of generalized tuberculosis in a girl of three, who a few days before death became icteric, developed petechial haemorrhages in the skin and bled from the mouth and bowel. An attempt to elicit the patellar reflexes produced large ecchymoses over both knees. The blood did not clot within fourteen days; fibrinogen was absent. No antithrombin could be demonstrated, and blood taken from the heart immediately after death showed only 14,600 platelets per c.mm. As at autopsy the liver was found to be riddled with caseous nodules; this organ was considered to be the source of fibrinogen. The thrombopenia was attributed to the effect of toxic liver products on the megakaryocytes and the bruising to increased fragility of the vessels.

Knauer (1927) recorded what he considered to be a case of purpura fulminans occurring in a previously healthy girl of six during the course of a mild attack of varicella. The skin became covered with ecchymoses the size of tea plates, there was haematuria and bleeding from the rectum. The bleeding time was normal but the blood failed to clot after three days. The blood fibrinogen was 0·015 gm. per cent. (normal 0·22–0·36 gm. per cent.). The platelets were 196,000 per c.mm. Following two transfusions of 180 c.c. and 120 c.c. of maternal blood the fibrinogen rose within four days to 0·27 gm. per cent. and the blood clotted in five minutes.

Convalescence was uneventful. In view of the absence of liver damage it was assumed that the fibrinogenopenia was due to temporary damage to the reticulo-endothelial system.

The case of Jürgens and Trautwein (1930) is of importance as suggesting an alternative source to the liver for the formation of fibrinogen. A fifty-two-year-old man gave a month's history of backache, anorexia and haemorrhage from nose, gums and bladder. The bleeding time was 30 minutes, there was no clotting after forty-eight hours. The blood fibrinogen was estimated to be less than 0·10 gm. per cent. (except terminally 0·25 gm. per cent.). Following a blood transfusion the bleeding time fell to 2½ minutes but the clotting time remained unchanged. Thrombin was formed in the blood in normal amounts. He died a month later from haemorrhage. Autopsy showed a carcinoma of the prostate with extensive bone marrow metastases. The liver showed subcapsular deposits but histologically was of normal structure.

An hereditary factor was first shown by Risak (1935). Under the title 'constitutional fibrinopenia' four cases in adults were published. The first case was that of a woman aged forty-one years who had bled from the gums and following slight trauma since girlhood. The blood fibrinogen was 0·018 gm. per cent., the platelets 144,000 per c.mm. Her son had a blood fibrinogen of 0·02 gm. per cent. In the second case a woman of twenty-two years gave a history of extensive bleeding from the skin and mucous membranes. The blood fibrinogen was 0·019 gm. per cent. and the platelets were 99,000 per c.mm. The mother had 58,000 platelets per c.mm. and a brother a clotting time of 13 minutes. The female members of the family had a haemorrhagic diathesis. The third case, a woman of seventy-one, had bled easily on injury since childhood. The blood fibrinogen was 0·018 gm. per cent., platelets 120,000 per c.mm., bleeding time 4½ minutes, clotting time 4 to 12 minutes. A son had a haemorrhagic diathesis.

The last case, also a woman aged thirty-seven years, had had menorrhagia since puberty and had had a haematemesis. Her fibrinogen was 0·018 gm. per cent., platelets 400,000 per c.mm., bleeding time 3 minutes, clotting time 5 minutes. The last two cases are remarkable in having a relatively normal clotting time with a low blood fibrinogen. Owing to the association of fibrinogenopenia with thrombopenia it was felt that the bone marrow played a particular rôle in the formation of fibrinogen.

A year later Wolff (1936) described a male infant aged four weeks, who developed bruising, anaemia and jaundice. Bleeding and clotting times were in the order of hours, platelets 296,000 per c.mm., fibrinogen 0·015 gm. per cent. Death occurred after a fortnight. Autopsy showed a greenish-yellow liver with no visible lobulation. A familial tendency to bleed was indicated by three sibs having died, each at the age of one year of 'blood spots.'

The first case in the English literature was that of MacFarlane (1938) who investigated a boy aged seven with intermittent haemorrhage since birth. The bleeding time was 30 minutes, there was no clotting within three weeks, and platelets were 110,000 per c.mm. No fibrinogen was detected in the blood. The addition of fibrinogen and thrombin to the patient's plasma and to control serum caused coagulation within 2½ minutes in both cases, from which the absence of any anti-coagulant was deduced. However, on adding fibrinogen to the patient's plasma, clotting took two hours as against sixteen minutes with control serum, which suggested that the formation of thrombin was also deficient. There was a strong family history. The father had a fibrinogenopenia (0·075 gm. per cent.), one sib had bled to death when ten days old and another had bled excessively following circumcision though his fibrinogen was normal. The parents were cousins. When seen a year later there was still no fibrinogen in the blood, though the platelets had risen to 425,000 per c.mm. and the bleeding time had fallen to 5½ minutes.

Schönholzer (1939) reported two cases, one seen by himself, the other by Fritzsche. He reviewed the literature. His case was that of a boy of twelve with a haemorrhagic diathesis since birth. He was admitted following a haematemesis and was so ill as to need immediate transfusion receiving 600 c.c. blood, after which the bleeding time was 30 minutes, clotting time 3¼ minutes, platelets 285,000 per c.mm. Within three weeks the blood had ceased to clot. He remained well for nine months when he was re-admitted with recurrent bleeding, received 350 c.c. blood after which the bleeding time was 2¼ minutes, clotting time 4¾ minutes, platelets 84,000 per c.mm. Thereafter the platelet count rose to 426,000 per c.mm. and the clotting time to infinity. No other abnormality in the blood was detected. Eighteen months later he was re-admitted with a fatal cerebral haemorrhage. The platelets were 334,000 per c.mm., the blood did not clot and contained no fibrinogen.

The case of Fritzsche was that of a girl aged two and a half who, having bled and bruised easily since birth, died from haemorrhage. Her blood did not clot; platelets were 180,000 per c.mm. No fibrinogen estimations were made. It was pointed out that small amounts of fibrinogen (it would be preferable to say blood) were sufficient to arrest haemorrhage. The amount of blood given in the first case was calculated to raise the fibrinogen to not more than 0·06 gm. per cent.

Schönholzer divided cases into congenital and acquired. The latter were secondary to some infective or toxic agent acting on the site of fibrinogen formation, which was considered to be the bone marrow. The congenital cases were further subdivided into congenital fibrinogenopenia, in whom the prognosis was good, and congenital afibrinogenaemia with a poor prognosis as regards longevity. Both congenital forms were hereditary; heterozygotic cases were supposed to produce fibrinogenopenia, homozygotic cases afibrinogenaemia. The factor was recessive, the condition occurring through the marriage of relatives, which explained its rarity. If, however, heterozygotic cases have to show some fibrinogenopenia, a certain 'penetration power' of the factor must be assumed; in other words the inheritance is not purely recessive but intermediate.

Glanzmann, Steiner and Keller (1940) described two cases, one congenital, the other acquired. The former was a boy of three with a haemorrhagic diathesis since birth. Admitted with traumatic bleeding from the mouth, the bleeding time was 5 minutes, clotting time more than twenty-four hours, platelets 35,000 per c.mm., fibrinogen absent. Haemorrhage was controlled with vitamins C and K and calcium gluconate. The acquired case was an eight-month-old female infant who developed a haemorrhagic diathesis in association with a

haemolytic anaemia, the liver and spleen being enlarged. The bleeding time was in the order of days, as was the clotting time. The platelets ranged between 187,000 and 116,000 per c.mm. The blood fibrinogen was absent, re-appearing slowly after treatment with vitamins C and K, calcium gluconate, congo red, campolon and citrated calf plasma by mouth.

It was concluded that two types of fibrinogen lack existed, congenital and acquired. In the former the deficiency was absolute and persistent, being associated with complete inability of the blood to clot and at times a transient thrombopenia. Attacks of bleeding occurred from time to time, due to trauma or to an unknown factor, large haematomata typically being formed. In the acquired variety the deficiency of fibrinogen was transient, was, according to these authors, associated with liver damage and the haemorrhages took a band-like pattern. Thrombopenia might also occur.

In view of the comparative rarity of cases of fibrinogenopenia and the divergent opinions as to its aetiology it was felt the following two cases were worthy of record.

Case reports

Case 1. HISTORY. M. E. R., a female infant, weighed 8 lb. when born on October 8, 1941. The mother was a primipara aged thirty-three. The pregnancy and labour were normal. The baby seemed to be normal at birth and took milk feeds well. After a few days she became fretful and refused to suck. About the ninth day she gradually became quiet though she seemed to be 'jumpy.' As she still did not feed she was admitted on the twelfth day (October 20, 1941) weighing 5 lb. 6 oz.

EXAMINATION. The baby appeared wasted and lifeless. The eyes were kept open, the pupils were small and reacted sluggishly to light. There was a variable squint; the eyelids twitched from time to time. The fontanelle was small but tense. A little blood oozed from the umbilicus. Temperature 97° F., pulse 130, respirations 40 per minute.

Lumbar puncture gave a blood stained fluid.

BLOOD PICTURE.

Hæmoglobin 56 per cent. Platelets 50,000 per c.mm.

Red blood cells 5,030,000 per c.mm. Haematocrit 48 per cent. Mean corpuscular volume $96\mu^3$.

White blood cells 12,750 per c.mm.

Differential count:

Neutrophil myelocytes 1 per cent.

Neutrophil meta-myelocytes 2 per cent.

Neutrophil polymorphs, non-segmented 4 per cent.

Neutrophil polymorphs, segmented 11 per cent.

Lymphocytes 74 per cent.

Monocytes 6 per cent.

Plasma cells 2 per cent.

Only giant platelets were present in the film.

Bleeding time 77 seconds.

Clotting time (capillary tube method): No clotting after 18 minutes.

Prothrombin time (one stage method):

Patient—No coagulation after 4 hours. (Control 22 seconds):

Serum albumin 4·17 gm. per cent. Blood fibrinogen 0·11 gm. per cent.

Serum globulin 1·10 gm. per cent. Blood calcium 8·10 mgm. per 100 cc.

On the day after admission large bruises appeared on the cheeks. Death occurred on the third day after admission.

AUTOPSY. On opening the skull there was a large amount of blood over the whole of the left vertex, over the right frontal lobe and on the median surface of the left hemisphere. There were no tentorial tears, but between the two tentorial layers on the left side were multiple lentil-sized haemorrhages. A considerable part of the right occipital lobe was destroyed by haemorrhage and numerous subependymal petechiae were situated in the right lateral ventricle. There were subpleural petechiae. No clots were found in the heart or in any of the great vessels or cerebral sinuses. The intima of the aorta and pulmonary artery was moderately icteric. The liver showed severe fatty changes. All other organs appeared normal.

HISTOLOGY. In the right occipital lobe a large area of brain tissue was necrotic and replaced by red blood corpuscles and débris. In the region of the posterior horn of the right lateral ventricle the blood vessels were distended and engorged with red blood corpuscles, there being numerous punctate haemorrhages. The erythrocytes were not confined to the adventitial spaces of Virchow-Robin but were also seen within the adjacent brain tissue. There was a distinct proliferation of glia cells in the subependymal layer. The ependyma itself was normal. Occasionally polymorphs and round nucleated cells were seen in greater numbers within a small haemorrhage.

The heart muscle fibres showed granular degeneration, the striation being very indistinct. In the liver were severe fatty changes of infiltrative type mainly in the periphery of the lobuli. The Malpighian bodies of the spleen were atrophic, the pulp was hyperplastic and cellular, the majority of the cells being large mononuclears. The venous sinuses were narrow and often empty. The kidney showed cloudy swelling mainly of the first convoluted tubules.

FAMILY HISTORY. In December, 1942, the parents were interviewed. They now had a second child aged four months who was healthy and thriving. His blood was examined which gave a clotting time of 1 minute 15 seconds, platelets 305,000 per c.mm., fibrinogen 0·22 gm. per cent.

The father and mother were the youngest and eldest respectively of families which were healthy, showing no tendency to bleed or bruise easily. The two eldest members on the father's side had both died at the ages of fifty-three and forty-one of cerebral haemorrhage. The elder had hypertension.

The father's blood, apart from a reduction in the platelets (150,000 per c.mm.), showed no abnormality. Blood fibrinogen was 0·31 gm. per cent. The blood pressure was 130/85 mm. Hg.

The father's brother aged thirty-six was also examined. He showed a normal blood count, a blood fibrinogen of 0·26 gm. per cent. and had a blood pressure of 140/85 mm. Hg.

The mother's platelets were reduced to 120,000 per c.mm. and her fibrinogen was 0·15 gm. per cent. The blood, nevertheless, showed no other abnormality, the bleeding time being 34 seconds, clotting time 2 minutes, prothrombin time 40 seconds (control 30 seconds). The platelets and fibrinogen were repeated three weeks later and were 220,000 per c.mm. and 0·15 gm. per cent. respectively.

Case **2.** HISTORY. D. C., a female, was born one month prematurely, weighing 6 lb.

The labour was normal, but the baby never seemed satisfactory, vomiting several times a day. On the tenth day she became jaundiced and although the depth of colour fluctuated, it gradually deepened. The urine became dark and the stools pale. At the age of two months two bruises were noticed on her knees. The following day she began to have bouts of screaming lasting intermittently for twelve hours. She then became weaker and was admitted (April 23, 1942).

EXAMINATION. A deeply jaundiced undernourished infant with slow grunting respiration. Pulse 72. There were twitching movements of the right arm and leg, the right side of the face being drawn up. The right eye showed coarse nystagmoid movements laterally and had a small reactive pupil. The left eye remained motionless in the mid line, the pupil was dilated and fixed, the eyelid was kept closed.

The fontanelle was tense. The liver edge was one to two finger breadths below the costal margin. Two bruises were present over the right knee.

The cerebrospinal fluid was blood stained.

BLOOD PICTURE.

Haemoglobin 84 per cent. Platelets 280,000 per c.mm.

Red blood cells 3,720,000 per c.mm. Reticulocytes 5·4 per cent.

White blood cells 14,500 per c.mm. Bleeding time 3 minutes 10 seconds.

Clotting time: No clot after 24 hours.

Prothrombin time: No clot after 30 minutes (control 25 seconds).

Blood fibrinogen: None found. Besides the Wu method for fibrinogen estimation, heating at 56 C., ammonium sulphate precipitation and the addition of fresh normal serum have been used.

60 c.c. of maternal blood were given intravenously, with 1 c.c. kapilon intramuscularly. The following day the prothrombin time was 30 seconds (normal control 20 seconds). The jaundice persisted, the liver became larger and firmer, the stools were persistently pale and contained no bile pigments [examined for bilirubin by the method of Malloy and Evelyn (1938), for stercobilinogen by a combination of the methods of Watson (1931) and Heilmeyer (1933) with omission of the ether extraction and for stercobilin and other pigments by spectroscopic and fluoroscopic examination of an acid-alcoholic stool extract after addition of zinc alcohol]. The patient died on August 1, 1942.

While in hospital further blood fibrinogen and 'prothrombin time' estimations were made on the following dates, control figures being given in brackets.

27/4/42. Prothrombin time 25 seconds (20 seconds).

29/4/42. Fibrinogen 0·29 gm. per cent.

7/5/42. Prothrombin time 20 seconds (20 seconds). Fibrinogen 0·34 gm. per cent.

29/7/42. Prothrombin time 45 seconds (23 seconds). Fibrinogen 0·34 gm. per cent.

AUTOPSY. A rather small, very hard dark green liver was found with the typical appearance of biliary cirrhosis. The gall bladder was normal in size, collapsed and contained a small amount of colourless fluid. The common bile duct was completely obliterated, the cystic and hepatic ducts were obliterated in their distal but patent in their proximal portions. The thymus was transformed into a soft haemorrhagic mass weighing 15 gm. There was an occasional haemorrhagic suffusion of the submucosa in the small intestine. Clotted blood, yellow pigment and thin spider-web-like membranes yellowish-red in colour were found on the internal surface of the dura mater over almost the whole of the left side of the vertex. The lateral ventricles were dilated. On the right side pus was found in the middle ear and there was necrosis of a considerable part of the petrous portion of the temporal bone.

HISTOLOGY. The liver showed a considerable proliferation of the cellular connective tissue in the interlobular spaces. The trabecular arrangement of the liver cells around the central vein was preserved in most lobuli, but often the connective tissue was seen growing into the lobuli, separating and isolating groups of cells. The bile ducts were proliferated and dilated, containing numerous bile thrombi. Except for the haemorrhage in the thymus nothing noteworthy was found in the other organs.

For fibrinogen, globulin and albumin estimations the method of Wu (1922) was used, for calcium estimation the method of Kramer and Tisdall (1921) and for 'prothrombin time' MacPherson, McCallum and Haultain's modification of Quick's one-stage method (1940) were employed.

Discussion

There can be little doubt that a deficiency of blood fibrinogen may be either congenital or acquired. Case 1 is considered to be an example of the former, Case 2 of the latter.

Characteristic of the congenital type is the tendency to bleed from birth, oozing from the umbilical stump being common. In those cases which survive, the bleeding is periodic, whereas the fibrinogen remains low or even absent. To explain the periodicity of symptoms, the existence of a second factor has been postulated. Rabe and Salomon thought there must be some change in the vascular permeability.

Several authors commented on the association of thrombopenia with fibrinogenopenia. A low platelet count per c.mm. was reported by:

Opitz and Frei (1921) 114,000.

Opitz and Silberberg (1924) 14,000.

MacFarlane (1938) 110,000.

Schönholzer (1939) 84,000 on one occasion only, terminally 426,000.

Glanzman et al. (1940) 35,000 rising to 275,000 with cessation of bleeding.

The figure of 50,000 in Case 1 may have contributed to the haemorrhagic tendency. Although the majority of the above figures are not low enough to explain the haemorrhagic manifestations per se, the thrombocytopenia may play a rôle in association with the fibrinogen deficiency.

Higher counts were found (296,000) by Wolff (1936) and (190,000) by Knauer (1927). The second case here reported had 280,000 platelets at the time of bleeding.

Opitz and Frei as well as Schönholzer showed that the platelets in their cases contained thrombokinase (more exactly Bordet's cytozyme). Functional platelet tests as described by Baar and Székély (1929),

by Morawitz and Jürgens (1930), by Jürgens and Naumann (1932), and recently by Wright (1941) were not used by these authors. That occasionally a functional deficiency of platelets without thrombocytopenia may be a cause of haemorrhagic disease of the newborn has been recently shown by one of us (Baar, 1941).

With regard to the co-operation of other factors in producing clinical symptoms and pathological coagulation in cases of fibrinogenopenia, Case 1 is of particular interest. The fibrinogen level, although definitely low, was higher than in any of the fibrinopenic cases described in the literature. Hatz and Kofanyi (1938) have reviewed all papers dealing with normal fibrinogen values up to 1938. In their table, figures obtained by refractometric or nephelometric methods may be disregarded as not sufficiently accurate. If only gravimetric and Kjeldahlometric methods are taken into account, 0·20 to 0·48 gm. per cent. (one figure 0·60) may be considered as the normal range for plasma fibrinogen. Peters and van Slyke (1931) give the figure 0·2–0·4 gm. per cent., Rappaport (1935) 0·2–0·4 gm. per cent. and Bendien and Snapper (1931) 0·25–0·40 gm. per cent. as normal. Gram (1922) and Starlinger and Windans (1928), who reported the largest series of normal and pathological cases consider 0·28 to 0·38 gm. per cent. and 0·22 to 0·36 gm. per cent. respectively as the normal range. Little has been done on the normal plasma fibrinogen of young babies. Crane and Sanford (1936) found, in an investigation on 131 infants aged one to ten days, a range of 0·22 to 0·36 gm. per cent. for the first and 0·33 to 0·50 gm. per cent. for the tenth days. From figures obtained in the Birmingham Children's Hospital by Kjeldahlometric and colorimetric methods it is believed that the plasma fibrinogen of young babies is within the normal adult range. Jürgens and Trautwein (1930) considered 0·15 to 0·12 gm. per cent. as the 'critical level' for fibrinogen below which the blood remained incoagulable. Risak (1935) rightly objected to this statement, reporting cases with lower fibrinogen figures and only moderately prolonged clotting time. The present case had a fibrinogen level of 0·11 gm. per cent. and yet the blood behaved like that of the severest fibrinogenopenia. There was no coagulation within four hours and only a tiny coagulum floating in the liquid blood some time afterwards. Such a clotting abnormality is never met even in the severest cases of prothrombin deficiency of the newborn. A prothrombin time of 4 to 6 minutes in the one-stage method indicates an extremely severe 'hypoprothrombinaemia,' and when once coagulation takes place the clot is of a perfectly normal appearance. In haemophilia, on the other hand, where a clotting time of several hours is often observed, the addition of a small amount of tissue extract is sufficient to correct the abnormality.

A calcium deficiency can not be responsible for the extremely long clotting time, the level being 8·1 mgm. per 100 c.c. and 9·6 mgm. per 100 c.c. respectively in the present cases, 10·5 mgm. per 100 c.c. in MacFarlane's and 12·0 mgm. per 100 c.c. in Schönholzer's cases. MacFarlane found that on addition of fibrinogen to his patient's blood the clotting time was still delayed as compared with a control. As he also proved that the amount of antithrombin was not increased, this must have been due to a diminished formation of thrombin, either from lack of prothrombin or of thrombokinase. Further support to this view is obtained from Schönholzer's observation that arrest of haemorrhage was achieved by the transfusion of a quantity of blood sufficient only to raise the fibrinogen level to 0·06 gm. per cent. From the data which Knauer gives, and assuming the blood he transfused contained 0·3 gm. per cent. of fibrinogen, it is estimated that relief from symptoms occurred with a fibrinogen level of 0·066 gm. per cent. Similar results were obtained in the second case here reported, when after blood transfusion the plasma fibrinogen was calculated to be about 0·05 gm. per cent.

If, in the first case where the blood fibrinogen was 0·11 gm. per cent. the prothrombin time were prolonged proportionally to the deficiency of fibrinogen, it should have been in the order of 60 seconds, providing all other factors necessary for clotting were present in adequate amounts. If it is assumed that there is no increase in antithrombin, then the greatly prolonged clotting time in the first case must be associated with another factor. As the blood calcium was normal and the thrombokinase was added in adequate amount, a quantitative or qualitative deficiency in the prothrombin is to be assumed. A direct estimation of the prothrombin level by a two-stage method was unfortunately impossible, as the baby died before a fresh fibrinogen solution could be prepared.

To throw some light on the discrepancies between the degree of fibrinogenopenia and the prolongation of clotting time it was decided to make some experiments in which constant amounts of fibrinogen were tested against various dilutions of thrombin or optimally incubated recalcified prothrombin solutions and vice versa. The fibrinogen solutions were prepared according to Herbert (1940) and purified by dialysis. The solution contained 0·4 gm. per cent. fibrinogen. Prothrombin and thrombin solutions were also prepared by the methods described by Herbert, the clotting time, however, was estimated by inclining the tube and two drops of fibrinogen solution were used instead of one. All estimations were made in a water bath at 37° C. The results of three experiments out of ten are reported below.

Experiment 1. Undiluted thrombin solution was added to increasing dilutions of fibrinogen in normal saline:

Fibrinogen diluted 1/1 produced a clot in 80 seconds.*
Fibrinogen diluted 1/2 produced a clot in 125 seconds.
Fibrinogen diluted 1/3 produced a clot in 165 seconds.

* The thrombin solution was prepared from stored plasma which probably accounts for the comparatively long clotting time.

Fibrinogen diluted 1/4 produced a clot in 175 seconds.
Fibrinogen diluted 1/5 floccules only in 243 seconds.
Fibrinogen diluted 1/6 floccules only in 285 seconds.

Experiment 2. Increasing dilutions of thrombin solution in normal saline were added to undiluted fibrinogen and to fibrinogen diluted 10 times.

Dilution of thrombin solution	Clotting time	
	Fibrinogen undiluted	Fibrinogen diluted 10 times
1/1	10 seconds	195 seconds
1/2	10 seconds	255 seconds
1/4	20 seconds	420 seconds
1/8	39 seconds	doubtful after 14 minutes
1/16	75 seconds (pellicle)	doubtful after 16 minutes

Experiment 3. To increasing dilutions of fibrinogen, thrombin has been added, which was obtained from 100 times and 200 times respectively diluted plasma optimally incubated after addition of calcium and brain extract.

Dilution of fibrinogen	Clotting time	
	Plasma diluted 100 times	Plasma diluted 200 times
0	30 seconds	30 seconds
1/1	40 seconds	30 seconds
1/2	40 seconds	30 seconds (soft)
1/3	60 seconds (soft)	70 seconds (soft)
1/4	80 seconds (soft)	210 seconds (partial and floating)
1/5	120 seconds (partial and floating)	indefinite

These experiments show that while within a certain range of dilutions the clotting time is roughly proportional to the concentration of the reacting substances, a dilution of thrombin to 1/2 may be without influence on the clotting time when the fibrinogen solution is undiluted, but cause a marked increase in the clotting time when a 10-times diluted fibrinogen solution is used. A dilution of fibrinogen to 1/4 prolonged the clotting time 2½ times when a prothrombin dilution 1:100 was used but 7 times when the latter was 1:200.

This limited compensation of a deficiency in one coagulation factor by another is, in principal, not new. Ziffren, Owen, Hoffman and Smith (1939) stated that ' when prothrombin falls below 30 to 50 per cent. a bleeding tendency appears. Above this level blood clots at a normal rate (6 to 10 minutes) suggesting that other factors vary to compensate for any prothrombin deficiency which may exist. Klinke (1938), who studied the kinetics of the thrombin-fibrinogen reaction, found a good agreement with a formula suggesting a self-accelerated enzymatic process only when both thrombin and fibrinogen were used in higher dilutions. It is, therefore, concluded that similarly as in the haemostatic mechanism, where one deficient factor may be compensated by another, there is also a mutual compensation among the factors concerned with one part of this mechanism, the coagulation of blood.

From these findings a serious objection arises against all one-stage methods of prothrombin estimation. It has to be realized that such a method gives only information about the clotting time in the presence of an excess of thrombokinase. The other known factors are fibrinogen, prothrombin and calcium. Any of these if deficient may cause a prolonged ' prothrombin time ' and fibrinogen being in excess may mask a moderate prothrombin deficiency. Fibrinogenopenia is, however, a rare condition and hypocalcaemia almost never causes a disturbance of coagulation. For routine estimations therefore the one-stage method will remain a useful measure of quantitative or qualitative prothrombin deficiency. More important is a therapeutic conclusion. It has recently become a habit to consider haemorrhagic disease of the newborn and hypoprothrombinaemia as synonymous. Vitamin K is used routinely and artificial feeding of the newborn has been recommended. Sanford et al. (1942), however, in a study of 1,600 newborn babies showed that, although the administration of vitamin K to the baby or to the mother before birth, raised the prothrombin level, it did not affect the frequency of haemorrhagic manifestations. Apart from the fact that the clinical results are not nearly as dramatic as the return of the ' prothrombin time ' to normal figures, the present observations give support to the view put forward in a leading article of the Lancet (1940), that the well established treatment by blood transfusions should not be abandoned in favour of vitamin K therapy.

The interrelationship between the various factors concerned with blood clotting is seen acting in a different manner in chronic pathological states in which a deficiency of one factor may be compensated for by another. This is seen in two cases of constitutional fibrinopenia in adults quoted by Risak, when in spite of a low blood fibrinogen (0·018 gm. per cent.), the clotting time was normal in one case and only slightly raised (4 to 12 minutes) in the other.

Case 1 is considered as congenital fibrinogenopenia because the haemorrhagic manifestations started soon after birth with oozing from the umbilical stump, the liver damage was of a common type and the mother had a low fibrinogen. Case 2 was obviously an acquired and transient afibrinogenia in a case of congenital obliteration of the bile ducts and biliary cirrhosis of the liver.

The lowering of blood fibrinogen as a secondary

manifestation naturally lead to speculation as to the site of its formation.

The rôle of the liver in the formation of fibrinogen is fairly well established. This was first suggested by Corin and Anlseaux (1894) who found disappearance of plasma fibrinogen in phosphorus intoxication. Isaac-Krieger and Hiege (1923) found fibrinogenopenia in diffuse liver diseases, often in icterus simplex and regularly in acute yellow atrophy. The significance of these findings is, however, somewhat shaken by the findings of Jacobi (1900), who demonstrated that the blood in phosphorus intoxication has fibrinolytic properties. Doyen's (quoted by Isaac-Krieger and Hiege, 1923) statement that the blood from the hepatic vein contains more fibrinogen than the peripheral venous blood and the experiments of Mann and Magath (1922), showing the disappearance of fibrinogen in hepatectomized dogs, can scarcely be explained in any other way than by accepting the liver as one site of fibrinogen formation. Glanzmann, Steiner and Keller (1940), from the consideration of their own case and those of Wolff, and Opitz and Silberberg, were of the opinion that acquired fibrinogen deficiency was associated with liver damage. In taking this view they ignored the cases of Knauer, and Jürgens and Trautwein and disregarded the opinion of Schönholzer, that in man no toxin acts solely on the liver. The case of Jürgens and Trautwein, although occurring in an adult, is important in suggesting the bone marrow as a site for fibrinogen formation. Müller (1905) found that after injections of dead bacteria the fibrinogen content of the bone marrow was greater than that of the blood. Keilhack, quoted by Jürgens (1938) estimated the fibrinogen of the red bone marrow of rabbits after washing out the blood and found it to be 1·095 gm. per cent. as compared with 0·296 gm. per cent. plasma fibrinogen. Jürgens (1938) mentions that at the height of a 'bathing' reaction there is a reticulocytosis associated with an increase of plasma fibrinogen. This, in association with the high plasma globulin figures in multiple myelomas, with the fibrinogenopenia in panmyelophthisis (aplastic anaemia) and with the observation of Jürgens and Trautwein in a case of acquired fibrinogenopenia, is suggestive of the bone marrow being a second site of fibrinogen formation. Experimental support for this conception was supplied by Jürgens and Gebhardt (1934) who found a rise in blood fibrinogen in dogs with Eck-fistula at the height of meat intoxication and in hepatectomized geese after pyrifer injections.

It is, therefore, not justifiable, in a case of liver disease and fibrinogenopenia, to assume without other evidence that the liver disease is the cause of the fibrinogenopenia. The case of congenital obliteration of the bile ducts is instructive on this account. After restoration of the fibrinogen to normal, the level remained constant until death three months later in spite of what must have been progressive liver damage. This led to estimations being made on cases of suspected hepatic disease. In the following cases, autopsy confirmed the diagnosis:

Case	Disease	Age at death	Fibrinogen estimated No. of days before death	Plasma fibrinogen gm. per cent.
P.W.	Icterus gravis	1 day	0	0·46
G.C.	Icterus gravis	5 days	2	0·42
R.B.	Congenital obliteration of bile ducts	4½ months	26	0·48
C.C.	Congenital obliteration of bile ducts	4 months	15	0·44
M.R.	Syphilis	2½ months	16	0·40
N.T.	Acute yellow atrophy	10 years	12	0·40

It is seen that severe liver disease may be without effect on the plasma fibrinogen.

Formation of fibrinogen in the liver and in the bone marrow is fairly well established. Damage of the bone marrow would also explain the comparatively frequent association of fibrinogenopenia with thrombocytopenia. A generalization, however, like that of Spadolini (1931–2), Campellone (1935), Leszler and Pauliczky (1933), Held and Behr (1934) and Risak (1935), who consider the whole reticulo-endothelial system as concerned with the formation of fibrinogen, is based more on speculation than fact.

Finally, one observation in the second case deserves some attention. A complete absence of fibrinogen was followed by normal amounts shortly after blood transfusion and injection of vitamin K. This may be a coincidence but Glanzmann et al. also observed a rise in fibrinogen after treatment which included vitamin K. The blood fibrinogen was, therefore, estimated over a long period in eight guinea-pigs. After a pre-experimental period four were injected with vitamin K. Following a further period to ensure that there was no alteration in the fibrinogen levels, all the animals were poisoned with phosphorus and the injections of vitamin K continued. No significant difference was observed between the two groups. This negative result is not conclusive as sufficient vitamin K may have been present in the food of both groups.

Summary

One case of congenital fibrinopenia and one case of transient afibrinogenia are described and the literature reviewed.

The relationship between prothrombin and other coagulation factors is discussed and experiments concerning this question reported.

The site of fibrinogen formation is discussed.

Experiments on the influence of vitamin K on fibrinogen formation were not conclusive.

Thanks are due to Dr. A. V. Neale for permission to publish the cases under his care and to Miss Finch and Miss Tonks of the Biochemical Dept. for the estimations.

Addendum.—Recently an additional case of congenital fibrinogenopenia was observed in an infant

with haemorrhagic disease of the newborn in which the findings gave support to the conception of a compensatory method in blood coagulation. On admission, the one-stage method of prothrombin estimation yielded no clotting in two hours. The fibrinogen level was 0·12 gm. per cent. After a blood transfusion and two injections of vitamin K the prothrombin time was sixty seconds but the fibrinogen remained unaltered.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE FIFTEENTH ANNUAL GENERAL MEETING

The Fifteenth Annual General Meeting was held in the Council Chamber, Town Hall, Llandudno, on Friday, May 14, 1943.

Business proceedings: The President, Prof. L. G. Parsons (Birmingham), was in the Chair and the following members were present.

Drs. Allen, Ashby, Bligh, Braithwaite, Bray, Capon, Collis, Ellis, Fleming, Gaisford, Graham, Jewesbury, Lapage, Lightwood, McNeil, Maitland-Jones, Moncrieff, Naish, Neale, Payne, Paterson, Perry, Potter, Scott, Sheldon, Smith, Spence, E. B. Smith, Watkins, Wilkinson, Williams, Winnicott, Wyllie.

Apologies for absence were received from the following members: Drs. Brookfield, Brown, Cameron, Cautley, Craig, Franklin, T. Y. Finlay, Harris, Hobhouse, Marshall, Morris, Nabarro, Ogilvie, Poynton, Pritchard, Rogers, Steen, Thursfield and Vining.

The Minutes of the last Meeting (Extraordinary Meeting) held on December 12, 1942, were read and confirmed.

The following were unanimously elected by ballot:—

President.—Professor L. G. Parsons (re-election).

Secretary and Treasurer.—Dr. Donald Paterson.

Executive Committee:

MEMBERS FOR LONDON: Dr. Alan Moncrieff. Dr. E. Bellingham Smith (in place of Dr. Wyllie).

MEMBERS FOR PROVINCES: Dr. J. C. Spence. Dr. A. G. Watkins.

MEMBER FOR SCOTLAND: Dr. G. Fleming (in place of Dr. S. Graham).

MEMBER FOR IRELAND: Dr. F. M. B. Allen (in place of Dr. W. R. F. Collis).

The President reported that following the resignation of Dr. Maitland-Jones from the secretaryship, the Executive Committee had placed on record their appreciation of his services during his period of office, and asked Dr. Maitland-Jones to accept the grateful thanks and appreciation of all members of the Association.

The Secretary submitted the report on the Executive Committee's activities since the meeting on December 12, 1942. It was resolved that a copy of this be circulated to all members (see below).

The Treasurer's Report was submitted and circulated showing a balance in hand of £89 13s. 3d. (including a sum of £56 16s. 5d. due from the Ministry of Health in respect of the Survey on Rickets) plus the sum of £100 invested by the Association in 3 per cent. Savings Bonds.

It was resolved that the date and place of the next meeting be left in the hands of the Executive Committee.

Dr. Sheldon said he would like to place on record the Association's appreciation of the activities of the Executive Committee during the past year.

The President asked Dr. Bray to accept the very grateful thanks of the Association for his most generous gift in endowing the Lectureship, to be known as the George Frederic Still Memorial Lecture, to be given bienially at the Annual Meetings of the Association.

REPORT OF THE ACTIVITIES OF THE EXECUTIVE COMMITTEE FROM DECEMBER 12, 1942 TO MAY 14, 1943, BY THE SECRETARY.

Mr. President and Gentlemen,

The last report of the Executive Committee was given on December 12, at the Extraordinary Meeting held at the Royal Society of Medicine on that date. Since then your Executive Committee has met on five occasions, four of these meetings being in London.

One of the current problems which your Executive Committee has been dealing with is **Neonatal Mortality.** A Joint Standing Committee has been set up, comprising seven members of the Royal College of Obstetricians and Gynaecologists and eight members of the British Paediatric Association; this Committee is now considering the Association's Report, and aiming at drawing up a fuller communication.

Vitamin D: Representatives of the Ministry of Food met your Executive Committee and discussed the new double dosage of cod liver oil, and the revision of the label appearing on the bottles.

Safe milk: Your Executive have continued to press for safe Milk.

Tuberculosis: The Association's Report on the Early Diagnosis of Tuberculosis in Childhood has been circulated to all members of the Association, and in addition to most of the children's hospitals, or departments of general hospitals, for the consideration of the medical committees. The report is being considered later this month by the Association of Tuberculosis Officers. We have already met the Invalid Children's Aid Association's representatives, and also representatives of the Hospital Almoners Association regarding this report, discussing in particular the convalescence of cases with a primary tuberculous infection.

The Executive look forward with much interest to the possibilities of closer co-operation with Public Health Services as a result of this report.

Rickets: You will be hearing details of the rickets survey later to-day. The investigation appears to have gone extremely well.

Royal College of Physicians: You have received a copy of the Memorandum prepared by the Executive Committee for the College on Paediatrics in the Curriculum. A deputation is to wait on the College at some future date.

Accommodation for neonates: You have also received a copy of a report on an ideal scheme for the accommodation of newly born infants in a maternity hospital. This report was prepared for the Goodenough Committee. You have also received a copy of the evidence prepared by Prof. C. McNeil for this same Committee.

Planning commission: You have also received a copy of the evidence prepared for this commission by Prof. C. McNeil.

Hospital architecture and the part it plays in the prevention of infection in children's wards: A questionnaire was drawn up and submitted to Prof. F. Fraser of the E.M.S., and this has been circulated to all the hospital superintendents in certain Sectors.

Rheumatism: The report on this subject has been received and circulated, and is to be considered at the present meeting (see below).

The relationship of clinical paediatrics and child psychology: The Executive Committee considered the report prepared by Dr. D. W. Winnicott, in collaboration with Major Mildred Creak and Dr. Alan Maberley (as circulated), and decided that this report should be considered at the Annual General Meeting.

George Frederic Still memorial lecture: The Executive Committee accepted on behalf of the Association, a sum of £350, which has been invested to yield a biennial income of twenty guineas. This gift was from Dr. George Bray, who in addition gave a further sum of £21 in order that the inaugural Lecture could be given this year. The Executive Committee feels that the Association is deeply indebted to Dr. Bray for his thoughtfulness and generosity.

Finally, it was with deep regret that the Executive received the resignation of Dr. A. Maitland-Jones from the Secretaryship, and a resolution, expressing their deep gratitude for his efforts on behalf of the Association was passed unanimously and placed on record.

DONALD PATERSON, Locum Secretary.

Scientific proceedings:—

1. DR. PEARSE WILLIAMS (London): 'The fate of the fat boy.' Observations on obesity in children recorded in papers on this subject have usually ceased at the age of 14 years. Records of boys attending a large secondary day-school in London whose progress has been followed up to the age of 16+, and in many cases 18 years have been analysed. In the ten years up to 1935 the average number of obese boys was 1·3 per cent. In the five years 1935 to 1940 the yearly average was 5·3 per cent. No explanation has yet been found for this marked increase.

Total fully observed: 58 of whom 31 per cent. were Jewish, evidence of a racial factor.

34·4 per cent. were from 10–20 per cent. overweight.

34·4 per cent. were from 21–30 per cent. overweight.

24 per cent. were from 30 per cent. upwards overweight between 12–14 years of age.

Between 16 and 18 years for the same group:—

24·1 per cent. were from 10–20 per cent. overweight.

13·8 per cent. were from 21–30 per cent. overweight.

8·6 per cent. were from 30 per cent. upwards overweight.

53·3 per cent. were within 10 per cent. of average weight.

Full genital development had taken place in 93·1 per cent. and was well advanced in 5 per cent. When an infectious disease, e.g. scarlet fever or other streptococcal infection, or diphtheria had preceded the onset of obesity the return to normal weight was definitely more slow. The vast majority of the boys had not received any special treatment.

[Note: It was resolved that a subcommittee be set up, with a view to compiling a revised height and weight table.]

2. DR. ELEANOR PECK (London) (introduced by DR. DONALD PATERSON): 'Some observations on the treatment of coeliac disease with parenteral B complex and crude liver.' Clinical and biochemical evidence has been offered by May et al. in Boston to show that normal fat and carbohydrate absorption can be restored in children with coeliac disease by alternate daily injections of 2 c.c. of crude liver extract and 2–4 c.c. of vitamin B-complex (Lederle) even when normal diets are maintained in periods varying from three to six weeks. A small number of cases are in the process of treatment in a like manner at the Hospital for Sick Children, Great Ormond Street. So far no deaths have occurred in the treated group which represent a variety of cases from the very early type to those of 4 to 5 years duration. Preliminary observation seems to show that definite clinical improvement takes place. Decreased irritability and improved emotional balance usually ensued first. The stools decreased in number and improved in appearance. The total fat content showed a sharp drop usually to within the normal range. Gains in weight and improved appetite, sometimes to the point of being ravenous, occurred, but sometimes the weight fluctuated or remained stationary. Abdominal distension did not vary greatly in the period of treatment. The length of treatment had to be varied with the clinical progress. Early cases seemed to do well with three weeks of therapy whereas the more stubborn cases required six weeks or even longer. At the completion of the period of parenteral therapy all patients have been given large doses of vitamin B-complex by mouth. The preparation used was B-plex (John Wyeth) up to 4 c.c. four times daily. The period of observation in these cases is short and it is not yet known whether in some cases the treatment will have to be repeated or further prolonged or if some type of maintainance therapy will have to be continued indefinitely at least during the period of growth, perhaps for the lifetime of the individual. At the present moment the results are sufficiently encouraging to warrant trial of the therapy elsewhere provided the necessary materials can be obtained.

3. DR. F. M. B. ALLEN (Belfast): 'Neonatal mortality in a maternity hospital.' In a review of 6314 babies born in the Royal Maternity Hospital, Belfast, in the four years 1939–42, there were 5621 full term with 61 deaths (mortality 1·07 per cent.) and 663 immature births with 126 deaths (mortality 19 per cent.). The mortality amongst immatures during these four years has been reduced from 29·8 per cent. to 16·3 per cent., having previously (1937) been 41·4 per cent. An analysis of the cause of death amongst the 61 full time showed congenital malformations: 26 (42·6 per cent.), intracranial haemorrhage: 14 (22·9 per cent.), infection: 7 (11·5 per cent.), respiratory distress: 5 (8·2 per cent.), icterus, mongolism and various: 9; in 126 immature births the cause of death was prematurity: 75 (59·9 per cent.), infection: 19 (15·0 per cent.), congenital malformations: 15 (11·1 per cent.), intracranial haemorrhage: 11 (8·7 per cent.), respiratory distress: 4 (3·1 per cent.), various: 3. Particular interest centred on the high proportion of congenital malformations, which accounted for 40 out of 187 deaths. It was shown that deaths amongst immature infants were not particularly related to the weight at birth, but that maturity was more important as regards survival; and also that the first twenty-four hours were especially critical in that more than half of the deaths occurred before the second day. It is suggested that there is a 'hard core' of neonatal mortality due to congenital malformations which is ineradicable and also that the co-operation of obstetricians should be sought to secure infants of maximum maturity consistent with the mother's safety.

4. DR. JANET GIMSON (London) (introduced by DR. DONALD PATERSON): 'Haemolytic disease of the new born (erythroblastosis foetalis)—its treatment with Rhesus negative blood.' Nineteen consecutive cases of erythroblastosis foetalis were treated and investigated with reference to the isoimmunisation theory of causation. The blood of all the mothers was Rh-negative, and that of the infants Rh-positive. Anti-Rh agglutinins were found in the mother's serum in all but one case. Differential diagnosis, from physiological jaundice or from congenital obliteration of the bile ducts, may be aided by serological findings. Eighteen cases required transfusion. Procedure varied as experience accumulated. Originally Rh-positive blood was given immediately the patient was admitted. In these, the first three cases, haemolysis continued or even increased. Further transfusion was soon necessary; then Rh-negative blood free of agglutinins was given. This does not prevent further haemolysis of the patient's erythrocytes. Blood is provided however which is not destroyed more rapidly than normal and on which the infant can live until the haemolytic process of the disease has

ceased. The later cases received Rh-negative blood exclusively; then more than two transfusions were unnecessary. Eleven cases received Rh-negative blood initially; eight of these required only one transfusion. No reaction occurred following Rh-negative blood in spite of using considerably larger volumes than previously (up to 300 c.c. by drip for a single transfusion); nor was there increase of jaundice. This compares favourably with previously published results; also with seventeen similar consecutive cases (1935–1941) treated by transfusion at the Hospital for Sick Children, Great Ormond Street. Here up to six transfusions were required in a single case. Six of the seventeen died; four remained alive without improvement in blood picture. The frequent occurrence of haemolytic reactions was probably due to the blood being Rh-positive, since this must have been incompatible. All nineteen cases of the 1942–43 series have been followed. Ages now range from 14½ months to 3½ months. Sixteen are normal. Three died of broncho-pneumonia, having regained and maintained normal blood pictures (two of these were mentally defective). Although a small number of cases have so far been studied, the results are encouraging.

(All serological tests were performed by Miss Boorman, Miss Dodd, and Dr. P. Mollison. A full report was published in the *British Medical Journal*, 1943, **2**, p. 293.)

5. Dr. R. C. Lightwood (London): 'Biliary obstruction in icterus gravis neonatorum.' The fundamental work on iso-immunization in erythroblastosis does not fully explain all the salient facts. For example, the antigen is held to reside in the red cells and a clash between it and the antibody derived from the mother, while explaining haemolysis, does not tell how either brain or liver cells come to be damaged. Also it is difficult to understand why the onset of anaemia is sometimes postponed even until late in the neonatal period, and delayed jaundice needs explanation as well as icterus persisting several months. The jaundice of icterus gravis is mainly haemolytic, though an obstructive element is sometimes present as well. When there is an obstructive phase it is usually early and evanescent. Three case histories were quoted showing that the onset of this phase may occasionally be delayed for a month or so, and that obstruction may persist for a considerable time. In the three cases jaundice and acholia lasted for 3½ weeks, 11 weeks, 3½ months. Although two recovered the one lasting 3½ months died. At autopsy the gall-bladder contained green bile which could be squeezed into the duodenum, the larger bile ducts appeared normal and the intrahepatic ducts contained bile-thrombi; liver cell damage and cirrhosis were present. Clinically, these cases of icterus gravis with persisting acholia soon come to resemble 'congenital' atresia of the bile ducts so that haematological and serological evidence is needed to prove the correctness of the diagnosis. But is it justifiable to presume that icterus gravis and atresia are unrelated? It is true that the biliary obstruction, believed to be due to highly viscid bile, usually disappears after a varying period but this might not happen always and then organization could follow. It may be recalled that Rolleston believed atresia of the bile ducts to be acquired, and he thought in terms of a maternal poison reaching the foetal liver by the umbilical vein. In this viscid, obstructing bile is a more likely cause for the type of atresia studied by Rolleston. It may also be concerned in sequential cirrhosis and it explains persistent jaundice as well as that which appears late.

6. Prof. G. B. Fleming (Glasgow): 'The incidence of tuberculous infection in a children's hospital.' A study of the incidence of positive Mantoux reactions in children admitted to the Royal Hospital for Sick Children, Glasgow, between the years 1938 to 1942 showed that there had been a slight increase in incidence in the age groups 0–4 years and 4–13 years in the year 1941 and a much more marked increase in 1942. This could not be attributed to deterioration in housing conditions as over-crowding was no greater during the war years than before its commencement, nor did it appear that overcrowding was greater among the positive reactors than among those giving negative reactions. As the increase in the incidence of tuberculous infection in children occurred a year later than in the adult population it is probable that it was due not to war stresses but to contact with infected adults in the home. It seems that the important factor in the spread of the disease is contact with carriers and consequently its spread should be controlled by isolation of infected persons as is done in other infectious diseases.

7. Dr. R. E. Smith (Rugby): 'The complications of mumps.' He stated that in the past there had been little thought about the life history of the virus in the incubation period, but Philibert's thesis that the virus entered the body through the conjunctiva, was incubated in the central nervous system, then spread generally and was excreted by the salivary glands, causing mumps, and occasionally attacking the pancreas or testicles and sometimes giving rise to definite evidence of cerebritis, made necessary a review of the conception that it was a droplet infection. Details of complications involving the genital tract were given. The high temperature associated with the orchitis, epidydimitis or hydrocoele was in contrast to that with the original mumps. Cerebritis was a rare complication, but in six of the twenty-two cases with complications there was a secondary rise of temperature not attributable to any definite cause. The lack of infectivity of mumps in the incubation period until the penultimate day and its rapid disappearance after the salivary gland returned to normal size all supported Philibert's theory that mumps was not incubated in the salivary gland but probably in the central nervous system as there was invariably a lymphocytosis in the cerebro-spinal fluid whether the patient had cerebritis or not.

9. Dr. D. W. Winnicott (London): 'Observations of infant behaviour during routine clinical examination.' In supporting his memorandum,* Dr. Winnicott attempted to illustrate what he meant by clinical psychology by describing the routine observation of infants who attend his medical out-patients' department. He observes what happens when the baby on his mother's lap is presented with an object. A right angled metal tongue depressor is placed on the corner of the table, and it is possible, he said, to predict what a normal baby will do in this set situation. [For details see *International Journal of Psycho-Analysis* (1941), **22**,, 229.] Dr. Winnicott claimed that it is possible to correlate the normal and abnormal behaviour of the infant in this simple situation with the complex relation of the infant to the people and objects in his environment, and also with physical symptoms such as inhibition of feeding, in so far as these are not based on definite physical diseases. The interrelation of infant feelings and the state and functioning of the infant body is something which is not properly recognized by paediatricians. Or at any rate the study of physical disease has far outstripped that of the equally important changes that are secondary to feelings, and to conflict of feelings. Dr. Winnicott asked for recognition of the importance of the study of infant and child feelings, and suggested that those who were in touch with young paediatricians should encourage some of them to take up this line of research. His memorandum * chiefly asked for the organization of a relationship between the B.P.A. and scientific psychological research.

* This refers to a report on the relationship between clinical paediatrics and child psychology which had been circulated to all members.

REPORT ON THE EARLY DIAGNOSIS OF TUBERCULOSIS IN CHILDHOOD

By Dr. WILFRID SHELDON (London—Chairman), Dr. STANLEY GRAHAM (Glasgow), Dr. WILFRID GAISFORD (Warwick) and Dr. REGINALD LIGHTWOOD (London)

1. Introduction: This report has been prepared because of the inadequate recognition of the importance of childhood tuberculosis and because of the increase of this disease during the early years of the war.

For the main part the rise in mortality has been caused by respiratory tuberculosis which has been most noticeable in young women between 15 and 25 years of age. Since October, 1941, a Committee of the Medical Research Council, set up at the request of the Minister of Health, has been investigating the causes of this increase. In the Summary Report referred to above, the Minister stated that 'the public should take such simple precautions as drinking only pasteurized milk, or boiled milk if pasteurized milk is not available, and do all in their power to prevent the spread of disease by droplet infection.' Before the House of Commons on June 30, 1942, the Minister said, 'We must review our general approach, and give greater practical effect to the need for early diagnosis.' Before the House of Lords on July 28, 1942, Lord Dawson remarked that the mortality from tuberculosis had increased by 13 per cent. in Great Britain since the war; that a novel feature in this war had been the extension in young children, particularly in the incidence of tuberculous meningitis, from which there had been an increased incidence of 50 per cent. A recent analysis kindly supplied by Dr. F. M. B. Allen (Belfast) showed that the infection in 72 per cent. of cases of tuberculous meningitis was due to the human bacillus. The Chief Medical Officer to the London County Council has recently reported that the death rate from pulmonary tuberculosis in 1941 as compared with 1938 has increased by 442 per cent. in children from birth to 4 years of age, and by 340 per cent. for children between 5 and 14 years of age (Daley, A., and Benjamin, F.: *Brit. med. J.*, 1942, **2**, 417).

2. Comments: (a) Tuberculous meningitis is an end result of infection occurring primarily in some other part of the body, principally in the respiratory or alimentary systems. Its prevention can only be carried out by preventing these primary infections, or, if they have occurred, by diagnosing them at an early stage and instituting appropriate treatment.

(b) Primary alimentary infection is acquired mainly from infected and unsterilized milk, and this source could be almost entirely eliminated by legislation, or greatly lessened by educating the public to drink milk which has been either efficiently pasteurized or boiled.

(c) Respiratory tuberculosis in childhood is acquired almost entirely by droplet inhalation from infected adults and adolescents, and occasionally from older children if they cough a positive sputum; but seldom from young children, partly because they do not tend to produce sputum, and partly because their intrathoracic lesion is seldom of an 'open' type.

Two points emerge from this:—First, that when an adult or adolescent is notified as suffering from pulmonary tuberculosis, examination of contacts must include children down to the age of infancy. Secondly, when a child is notified as suffering from intrathoracic tuberculosis, adults with whom he or she has been in contact must be examined, not merely to ascertain the source of infection, but to prevent this source from infecting other children, e.g. infection in a school child may require the examination not only of the relatives but also of the school teacher, as a possible means of protecting other children in the class.

(d) For the most part, the diagnosis of intrathoracic tuberculosis in infants and children is made by hospital physicians and general practitioners. Whether such children are examined by their general practitioner or at a hospital is, however, a purely fortuitous matter, depending upon the whim of the parent who may or may not consider the child sufficiently ill to seek advice. There is no machinery by which children exposed to infection have to be taken for examination, beyond that of the tuberculosis officer, and at the present day, this machinery works, as it were, in a watertight compartment, without involving either the hospital paediatrician or the general practitioner.

(e) A more widespread enquiry for child contacts is required than is at present being carried out, for there is no doubt that many young children, infected by adults, elude examination by the tuberculosis officer. The success of such enquiry depends largely upon the information gathered by the tuberculosis nurses; the particular ease with which young children become infected should be brought to their notice, and they should be encouraged to widen their search beyond the immediate family circle when conducting the enquiry for child contacts.

> *Example:* Three young boys, brothers, spent their nights during the winter of 1940/41 in a private air-raid shelter with their neighbours. The middle-aged neighbour father had phthisis and had infected his grown-up son and daughter, all three of whom were detected and dealt with by the tuberculosis officer. The three young brothers entirely escaped examination until by chance they were brought to hospital when all three were found to be infected.

(f) The time for which contact is necessary in order for infection of a child to occur is shorter than is often realized, and may be no longer than a day. This should be borne in mind when conducting an enquiry for child contacts.

> *Example:* Two young children, evacuated to the country, spent one night in a house, with a phthisical aunt, who went next day to a sanatorium. Both children became infected, and one died of miliary tuberculosis.

(g) A high proportion of children, suffering from erythema nodosum and phlyctenular conjunctivitis, indicate by these disorders their recent infection with tuberculosis and therefore these illnesses often lead to the detection of early tuberculosis. These illnesses are not notifiable, and yet some simple machinery is required by which children suffering from them may be brought to the notice of the tuberculosis officer in order to undergo an investigation by him.

(h) The pathological process in intrathoracic tuberculosis in childhood differs from that in the adult. The latter tends to have a local lung lesion, spreading centrifugally, and progressing to cavity formation, with the production of a positive sputum; the former has a small primary focus in the lung, which seldom progresses to cavity formation, but instead the disease spreads along the lymphatics to the bronchial and hilar lymphatic glands. The primary focus in a child is seldom large enough to produce physical signs, and infection of the hilar glands is notoriously difficult to detect by clinical means alone.

(i) To be expert at the diagnosis of adult pulmonary tuberculosis does not necessarily denote an equal skill in discovering intrathoracic tuberculosis in childhood. Further, to make the most of the clinical examination of infants and young children, practice in handling them is essential. Although paediatricians have an unrivalled experience in handling sick children, there are not enough trained paediatricians at the present time to undertake the examination of child contacts on a national scale, and in any case, this work falls properly within the province of the tuberculosis officers.

The objective—namely, the early diagnosis of tuberculosis in children—would be placed within easier reach if a closer co-operation could be arranged between the tuberculosis officers and paediatricians. Broadly speaking, no such co-operation exists at present.

3. Methods of investigation of children : For the early diagnosis of intrathoracic tuberculosis in children, the following methods need to be employed :—

(a) CLINICAL EXAMINATION: An examination of the whole child is required, as the symptoms of intrathoracic tuberculosis may also arise in other conditions, e.g. chronic dyspepsia, chronic infections in the upper respiratory tract. It must be acknowledged that however thorough the clinical examination, the diagnosis of intrathoracic tuberculosis by clinical examination alone presents great difficulty, and is indeed often impossible.

(b) TUBERCULIN SKIN TESTS: Whatever test is employed, whether the Mantoux intra-dermal test or the Vollmer patch test, their importance in the diagnosis of tuberculosis in young children is undoubted, and is fully accepted by paediatricians. Although these tests, as with all other investigations, are liable to technical errors, and the significance of a positive reaction varies with the age of the child, the technique is relatively simple, and the significance of a positive reaction, at any rate in young children is straightforward. It is our opinion that the value of these tests in children is in general under-rated and that because of this many infected children escape diagnosis at a stage of their disease when recovery should be possible. We wish to emphasize that these tests should be used far more widely, and recommend that every facility for carrying them out should be placed at the disposal of medical officers in charge of child welfare clinics, and of school medical officers.

(c) X-RAY EXAMINATION OF THE CHEST: An indifferent x-ray of the chest is worse than useless, as it may actually be misleading. Although it is impossible to get far with the investigation of child contacts without x-rays, their efficient use demands three qualities :—First, the apparatus must be sufficiently powerful to take a good picture with a short exposure, for young children may neither lie still nor hold their breath. Second, the radiographer needs to be experienced in the handling of children if satisfactory films are to be obtained without waste of material. Third, the interpretation of the film must be made by someone conversant with the picture of tuberculosis as met with in childhood ; in practice, the opinion of a radiologist, provided he has had particular experience in the subject, would be of great help to the physician—whether paediatrician or tuberculosis officer—in his full assessment of any individual case.

(d) GASTRIC LAVAGE FOR THE DISCOVERY OF SWALLOWED TUBERCLE BACILLI: Whilst the finding of tubercle bacilli in sputum is of supreme diagnostic importance in an adult, this is not the case with children, who only seldom expectorate. To postpone the diagnosis of intrathoracic tuberculosis in a child until tubercle bacilli have been found, would be courting disaster for the patient. Tubercle bacilli can sometimes be recovered from gastric washings in a tuberculous child, and this examination is of particular value in infants, in whom the technique is relatively easy, and also in an older child, if there is reason to suppose that he or she is disseminating infection. Unlike the previous investigations, the examination of gastric washings, entails admission to hospital, but is only required in a few selected cases.

(e) ERYTHROCYTE SEDIMENTATION RATE: This test, which is not strictly an aid to diagnosis, is of value when estimating the degree of activity of a tuberculous lesion. By repeating the test at intervals, a useful indication is given of the progress of the lesion. Seeing that the sedimentation rate is influenced by other infections, the test may be misleading unless a complete clinical examination has been made. Should special clinics for the examination of child contacts come into being, they ought to be equipped, and the personnel trained, so that the above investigations could be efficiently carried out—with the possible exception of examination of gastric washings, for which special facilities would be required.

4. Notification: The notification of tuberculous children is in a thoroughly unsatisfactory position. Some of the reasons for this are :—

(a) Physicians hesitate to notify because they realize that the majority of children, in whom the diagnosis is made at an early stage of their infection, recover completely, but once they are notified, the stigma of tuberculosis attaches to them long after recovery has been made, and is likely to lead to a persistent, although unnecessary, imposition of invalidism.

(b) Notification usually implies that the local authority shall undertake treatment. The difficulty at once arises that the local authority does not possess the accommodation required for the treatment of tuberculous children. They are unsuitable for treatment in adult sanatoria ; ordinary convalescent homes will not accept children labelled as tuberculous. A position has been reached, therefore, where the very fact of notification makes it often extremely difficult for either the doctor concerned or the tuberculosis officer, to arrange suitable treatment. Believing that the risk that a young child with a primary lung infection will infect others is remote, the avoidance of notification enables these children to obtain their necessary convalescence under other guises.

(c) It has already been pointed out that the diagnosis of intrathoracic tuberculosis in children, on clinical examination alone, is often impossible, although the result of skin tests and x-ray findings may leave no reasonable doubt about the diagnosis. If the notification of anyone 'suffering from tuberculosis' is statutorily required, should a child in whom evidence of tuberculosis rests on :—(1) a positive skin test, or (2) a positive x-ray finding, or (3) a combination of (1) and (2), but in each instance without physical signs, be notified?

(d) The need for notifying children suffering from erythema nodosum and phlyctenular conjunctivitis to the tuberculosis officers has already been pointed out; yet seeing that only a percentage of these children—albeit the majority—are tuberculous, they should not have to be labelled as tuberculous in order to have them investigated by the tuberculosis officer.

5. Co-operation between paediatricians and tuberculosis officers: Closer co-operation between Paediatricians and Tuberculosis Officers is highly desirable and is long over-due. The following suggestions are put forward as a means of bringing about such co-operation:

(a) Special clinics for the investigation of child contacts are required. Whenever possible these should be set up at children's hospitals, or in the children's department of general hospitals, because it is here that the necessary facilities are available, e.g. radiographers experienced in x-raying children, x-ray apparatus suitable for children, in-patient accommodation for special investigations if required, and the services of a visiting paediatrician. It would also avoid the attendance of children at an adult tuberculosis clinic, where unless special precautions are taken, or a special session is reserved for children, the risk of their becoming infected is great.

(b) The children who should attend these clinics would be discovered through the machinery of the tuberculosis officer.

(c) The children at these clinics should be examined by the tuberculosis officer, and each hospital would have to consider the advisability of affiliating the tuberculosis officer in some suitable manner to the medical staff.

(d) The ultimate responsibility for the work at the clinic, when set up at a hospital, should rest with the paediatrician, on whose opinion the tuberculosis officer should be able to call in any doubtful or difficult case. Where clinics are held at hospitals with medical schools, the medical students should attend for instruction. It may be mentioned that such an arrangement bears comparison with the L.C.C. Rheumatism Clinics for children maintained before the war at some of the London hospitals.

(e) Short courses of instruction in childhood tuberculosis should be given by paediatricians and should be available to tuberculosis officers as well as to general practitioners. Arrangements for these courses might possibly be made through the British Post-Graduate Medical School.

6. **The general practitioner:** In the attack against respiratory tuberculosis in children the part to be played by the general practitioner cannot be overlooked. In many districts, especially country districts, the responsibility for finding and examining child contacts will be his. It should be the duty of the county tuberculosis authority to place within reach of the general practitioner the means for conducting an efficient examination, including skin tests, as it must be the duty of paediatricians to see that men going into practice are taught the need for, and methods of examining child contacts. The attendance of general practitioners at post-graduate courses of instruction in this subject has already been mentioned.

7. **Accommodation for treatment:** Although this report is concerned with diagnosis, it must be pointed out that a widespread enquiry into child contacts would give rise to a large number of young children found to be suffering from a primary tuberculous infection and the care of these children would create a problem of its own. It must be recognised that for many children the outcome of their illness is decided in the first few months after infection, from which it is clear that early diagnosis can only lead to satisfactory results if followed by prompt and efficient treatment. Further, the majority of children needing treatment will be of the infant, toddler and pre-school age group. For the majority of them treatment away from their homes would be required, and to nurse them through their illness in hospital wards would overload the cot capacity of the hospitals ; nor is the environment of a hospital ward the best setting for their recovery. To nurse them in adult sanatoria is unwise owing to the risk of further infection ; the nursing staff of these establishments is not particularly trained in the nursing of children and the accommodation that would be needed is not available. To meet this situation, convalescent homes in the country—' preventoria '—should be established and some of the existing convalescent homes possibly be given over for the care of these children. In addition to children showing a primary complex, those who are suffering from the various allergic manifestations (erythema nodosum, epituberculosis, pleurisy with effusion, phlyctenular conjunctivitis) should be eligible for these homes.

8. **Summary:** (a) In order to improve the present position with regard to the early diagnosis of intrathoracic tuberculosis in children, a much greater effort must be made to discover and examine children who have been exposed to cases of pulmonary tuberculosis of the adult type.

(b) To discover these children the machinery used by the tuberculosis officers should be employed.

(c) Special clinics should be set up for the examination of child contacts.

(d) Such clinics, whenever possible, should be set up at children's hospitals or children's departments of general hospitals and should be under the direction of a paediatrician.

(e) The investigation of children at these clinics should be carried out by the tuberculosis officer who should be affiliated to the medical staff of the hospital. It is considered that if co-operation on these lines could be established, some of the problems arising out of notification would find an automatic solution.

(f) Short courses of a post-graduate type, devoted to the subject of intrathoracic tuberculosis in children should be conducted by paediatricians.

(g) A corollary to the previous recommendations must be that convalescent homes in the country should be used for the care of children suffering from primary tuberculosis.

9. **Recommendations to the executive committee of the British Paediatric Association:** (a) This report be referred through the Chief Medical Officer of the Ministry of Health to the Minister, with a request for his assistance in putting the recommendations into practice.

(b) Copies of this report should be sent to the Association of Tuberculosis Officers, the Society of Medical Officers of Health, the British Post-Graduate Medical School, the Co-ordination Committee of the London Children's Hospitals, the Children's Hospitals and those General Hospitals having Children's Departments throughout the country.

(c) The executive committee should ask for a conference with a similar committee from the Association of Tuberculosis Officers in order to discuss the whole question of notification of tuberculosis in children. If at such a conference, agreement can be reached that difficulties exist and if practical solutions to these difficulties can be found, the combined committee should then approach the appropriate authority.

(d) In addition to a conference on notification, a conference embracing the other suggestions in this report will be required between the British Paediatric Association and the Association of Tuberculosis Officers and any other authorities concerned. If co-operation at such a conference can be obtained, the executive committee should then be prepared to approach the medical boards of hospitals containing a paediatric department to put this scheme before them.

(e) The executive committee should consider the advisability of publishing, at the appropriate time, as much of this report as they think fit in the medical press.

ARRANGEMENTS FOR NEWLY BORN BABIES IN MATERNITY HOSPITALS

By CHARLES McNEIL (Edinburgh—Chairman), N. B. CAPON (Liverpool—Secretary), W. R. F. COLLIS (Dublin), S. GRAHAM (Glasgow) and A. MONCRIEFF (London)

(Report prepared by the British Paediatric Association, at the request of the Goodenough Committee)

An ideal plan, assuming no restrictions, financial or otherwise ; the chief aims being to safeguard the health of newly born infants, and to ensure that each baby on discharge from the hospital, with its mother, is breast fed, is in the care of a mother who has been instructed and is competent in the handling of her infant and that the mother is happy and anxious to have a family of reasonable size.

1. General comments: (a) All the newly born babies (healthy, immature and sick) in a maternity hospital should be in the charge of a paediatrician who is experienced in this work, and who shall be a full member of the staff and advise on the general paediatric policy of the hospital. He should act in close co-operation with the obstetricians and with the public health medical officers of the district. The assistance required by the paediatrician will naturally depend upon local conditions, such as the size of the hospital ; the minimum would be one assistant paediatrician (undergoing training in neonatal work), together with the services of one or more resident medical officers who must have had previous paediatric experience. One or more infant welfare clinics in the personal charge of paediatricians should be held in hospital for the benefit of mothers and babies, who should be instructed to report periodically after their discharge, if living in the vicinity of the hospital. A number of social workers and health visitors should serve on the staff of these clinics to visit the patients in their homes in order to ensure adequate supervision. Mothers and their babies from outlying districts would obviously attend the child welfare clinics nearest to their homes. Special attention at these clinics should be given to premature infants, and a liaison with the centre for prematures (see later) should be established.

(b) The above neonatal service should be part of the department or institute of paediatrics and should be fully used for research and for the teaching of post-graduates, undergraduates, nurses, health visitors and mothers.

(c) Even in an ideal plan it would be unwise, indeed impossible, to lay down hard and fast rules regarding some of the details of accommodation, etc., because local conditions must be taken into account. Thus, in some maternity hospitals, a much higher percentage of abnormal obstetrical cases occur than in other institutions, and in the former, it is to be expected that there will be a higher proportion of abnormal newborn babies. We should, however, record what we believe to be the basic needs, in so far as the infants are concerned ; these are:—

(i) Every mother should be in a separate cubicle or room, large enough to accommodate her and her baby.

(ii) There must be a sufficient number of day and night nurses properly trained in the care of newly born infants and able to impart their knowledge to trainees. The health of the nurses must be supervised, and in the event of a nurse developing an infection such as a head cold, sore throat, diarrhoea or the like, she should not be allowed on duty until she is passed free of infection by the physician in charge.

(iii) Proper supervision of infant feeding, with special attention to breast feeding.

(iv) There should be established a special centre for the care of immature babies born both within the hospital and from the district. This is dealt with more fully under 5.

(v) The formation of a breast milk ' pool ' or ' bank ' in the hospital for the in-patients and out-patients who are unable to receive breast milk from their mothers.

(vi) A properly equipped milk kitchen in which artificial feeds can be prepared and nurses taught the methods.

(vii) Adequate laundry arrangements for the washing and sterilizing of napkins. Suitable machinery should be installed.

31st Jan., 1943.

2. Should babies be accommodated with their mothers or in special nurseries? We believe, as stated in (i) above, that each mother should be in a separate cubicle or room large enough to accommodate her and her child. For convenience in administration cubicles would be grouped into wards of 8 to 20 and the walls between adjacent cubicles would be glass in order that patients would not feel isolated. Babies would receive all necessary attention, e.g. bathing, clothing and feeding in the cubicle, and there would need to be in each cubicle adequate provision of equipment for the nursing care of the child, for instance, bath, immersion and low-reading clinical thermometers, hot rails, trolleys, cupboards, weighing scales, closed receptacles for soiled napkins, etc. A gown and mask should be worn by every person entering a cubicle (doctors, nurses, students, visitors). Healthy infants should be in the care of nurses who are responsible also for the mothers, but the sister and staff nurses should be on the Sick Children's Nurses' Register, as well as holding the certificate of the C.M.B. Extra accommodation will be necessary for certain babies who, for various reasons may require to be removed from their mother's room, e.g. mother's illness, bad congenital abnormality in the infant, crying infants, and so forth. Accommodation for such infants would of course be of the cubicle type.

3 and 4. What nursery accommodation should be provided for sick babies and what isolation facilities should be provided? Some paediatricians consider that maternity hospitals should be adequately staffed and equipped to enable them to deal with most of the ' medical ' diseases occurring during neonatal life ; other paediatricians hold the view that all but the most trivial cases of neonatal illness should be removed to a children's hospital and that these institutions should have a number of rooms available for the reception of the mother as well as her child. If the first view is accepted it would naturally follow that maternity hospitals must provide accommodation for sick babies, and also have isolation facilities. We consider that an infant population of 75 would probably require 10 to 15 cots in a sick nursery or bay, and they should be isolated in cubicles with glass fronts on to a corridor and be air-conditioned. There should be a wash-hand basin in each cubicle ; and arrangements for darkening a cubicle when necessary. Piped oxygen is an advantage. Sick infants should have a special staff (day and night) of nurses, trained as sick children's nurses, and the mask and gown system must be strictly used. Pupil midwives should receive an adequate training in these nurseries. A medical examination room adjacent to the sick bay would be an advantage.

5. Arrangements for prematures: It is necessary to have cubicles for premature infants, and the number will depend upon the type of obstetrical work done. In some maternity hospitals which deal with a relatively high proportion of abnormal cases, the prematures may be 10 per cent. to 20 per cent. of the total infants ; in hospitals which accept a higher proportion of normal cases, the prematures will be 5 to 10 per cent. of the total infants. In the premature cubicles there must be special provision for conditioning the air (temperature and humidity), and some of the cots should be of special type. The staff must be adequate in number (day and night), the seniors being specially trained in the care of prematures, and not engaged upon other duties. Pupil midwives should receive instruction in the nursing of immature babies. Most of the points referred to in this statement are also dealt with, in some cases more fully, in the Report of the sub-Committee on Neonatal Mortality (*Arch. Dis. Childh.* 1943, **18**, 62), which should be studied alongside this statement.

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